UK Biopharma - Adapting to a changing landscape to deliver a better global future

1. Introduction

The UK Referendum decision on EU Membership has opened a new chapter in the future of the UK, both socially and economically. The challenge is that we must now write that chapter with little precedent from which to learn. This means the Government urgently needs to develop a comprehensive industrial strategy for the life sciences to secure the opportunities outlined in this paper that will benefit healthcare and patients. Critically, it must also appoint a significant and dedicated champion to deliver it.

The paper is therefore an attempt to determine what a constructive implementation of the Referendum result could mean for the UK and EU biopharmaceutical sectors and to develop practical responses and actions. *A priori*, it proposes ideas for opportunities (some of which have already had a long latent period) that the UK could exploit to its advantage on a global stage, and critically, to show how the UK remains fully open for biopharmaceutical business. These include ideas to minimise anything that could make the UK a less attractive place to do business and, in parallel, to "up the ante" on the factors that work well and can be improved further.

"In the middle of difficulty lies opportunity" (Einstein).

1.1 The Immediate Future

The UK Government is expected to invoke Article 50 of the Lisbon Treaty by notifying the EU Council of its intention to leave the EU by early 2017. If no agreement is reached within two years of the notification, the EU Treaties shall cease to apply to that country. The two-year period may only be extended if the European Council unanimously agrees.

With a Prime Minister now firmly in No 10, the timing and tenor of the Article 50 negotiations are bound to be strongly driven by her outlook and she has said 'Brexit means Brexit'.

There are many potential options that might be negotiated – some of these options may not yet exist. However, the three most discussed trading routes for the UK to pursue, once Article 50 has been triggered, are:

- The European Economic Area ("EEA");
- The European Free Trade Association ("EFTA"), the Swiss route;
- The World Trade Organisation ("WTO").

Under the EEA route (current members Norway, Iceland and Liechtenstein), the UK would have to enter into the wide-ranging EEA agreement with the EU, under which, it would retain free access to the EU market for goods and services.

However, in return for such access, it would likely have to continue to accept free movement of labour, a key issue in the Leave campaign. Some have argued that the UK should negotiate to join the EEA with its access to the single market, but with a right to control immigration. However, the EU has made clear in the past that the four fundamental freedom of movement pillars are non-negotiable.

Switzerland is in an unusual position. It is a member of EFTA, but the only one of its four members to be outside the EEA (the others being Norway, Iceland and Liechtenstein above). Instead it has negotiated six bilateral agreements with the EU and one of them includes the free movement of labour.

This raises the same problem as the EEA over immigration. Indeed, EU immigration in Switzerland has been relatively higher than in the UK. In a recent Swiss referendum, the voters opted to restrict EU immigration to quotas from 2017, but the EU has refused to accept this decision and has threatened to suspend all six bilateral agreements.

If control of immigration continues as a stumbling block, the UK would be forced to agree to WTO rules. As the UK is currently only a WTO member through the EU, it would have to join the WTO and then enter separate trade agreements with the desired trading partners, including the EU. An example of this approach is Canada's 2014 Comprehensive Economic and Trade Agreement (CETA) with the EU. It is worth noting that this took five years to negotiate, and is expected to take another two years to be ratified by EU members.

1.2 Analysis

The Brexit vote has created an environment of uncertainty for our Members – particularly in respect of the future of research funding and of free movement for scientists who contribute to research. Leaving the European medicines regulatory regime would exacerbate this uncertainty and, if the Government prioritises stability, European Economic Association (EEA) membership would be the best 'Brexit scenario' to pursue.

If the UK Government chooses a looser arrangement with the EU than EEA or EFTA membership, then it is too simplistic to say that the pharmaceutical sector is faced only with risks. There are enormous opportunities that must be explored and the pharmaceutical industry must contribute now in a positive way to the Government's thinking in this area.

Just one example is the potential to enhance significantly the potential of the MHRA's Early Access to Medicines Scheme (see below).

2. Areas for consideration – Impact, Risk Mitigation and Opportunities

2.1 The Regulation of 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) appoints a Rapporteur and Co-Rapporteur to review the 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 'concerned 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. An MA applicant or holder must be 'established' in the EU.

In addition 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; 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. Imported products also need a release site within the EU.

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.

2.2 Planning for Regulation Post-Referendum

The EMA and other EU 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 be expected to move its headquarters out of the UK and relocate in one of the remaining EU countries. Further, rapporteurs from the UK will not be accepted.

However, as part of the forthcoming negotiations, it might seem sensible for the UK to agree a Mutual Recognition Agreement (MRA) - such agreements already exist between the EU and Switzerland, Canada and Australia.

The EMA is likely to regret the loss of the UK competent authority, the Medicines and Healthcare Products Regulatory Agency (MHRA). This is because 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. Also, in the event of an Mutual Recognition Agreement, it is doubtful that a world-leading Agency, such as the MHRA, would be willing to simply "rubber-stamp" others' opinions. We would therefore strongly encourage the MHRA to be enabled to develop national policies in key areas where there are currently regulatory bottlenecks, which, when mature, could be applied more globally. Examples include;

2.2.1 The Clinical Trials Directive; looking objectively at where it could be reformed to reduce or remove areas of overt bureaucratic burden on all organisations that conduct clinical research. Since its introduction, the requirement for "paperwork" has often been cited as a cause of escalating costs and declining attractiveness to both the UK and the wider EU as a place to site clinical research…or…."Europe's gift to America", as an FDA official once put it.

2.2.2 Drug/device combination products; these products are at the borderline between being medicinal products and medical devices, where currently two sets of non-aligned regulation exist. The MHRA should be allowed to explore creating regulations that bring together elements from both to give clear guidance for companies.

2.2.3 The regulation of companion diagnostics; A key issue amongst regulators across Europe is whether companion diagnostics and other medical devices should be regulated in similar ways to medicines, particularly with regard to in-vitro diagnostic (IVD) tests. Traditionally the regulation of medical devices has remained separate from pharmaceuticals. With the trends towards personalised medicines, Health Technology Assessment (HTA) bodies are investigating combinations of individual medicines and IVD tests for detecting those patients most responsive to them. These assessments, however, do not cover the design, materials and manufacturing process of the equipment – which would potentially affect the accuracy and reliability of the equipment. New proposed European regulations will look to harmonise the assessment, to resolve these issues. (http://www.pharmtech.com/regulation-medical-devices-and-companion-diagnostics)

2.2.4 Advanced Therapy Medicinal Products (ATMPs); are medicinal products which are either a gene therapy or somatic cell therapy medicine or a tissue engineered product. These type of products evolve at a very fast rate. Currently, the EU regulation for these type of products is complex. The EMA's Committee for Advanced Therapies (CAT) is responsible for assessment and following scientific developments in the field. There is potential for simplification of this regulation, using the MHRA as a national lead on these type of products as an exemplar pilot. The MHRA should be able to develop regulation to reduce

the 'norm' of use by hospital exemptions whereby unlicensed ATMPs can be made available in the UK for a specific patient. The UK should build on the presence of the Cell and Gene Therapy Catapult, the independent centre of excellence for the UK cell and gene therapy. With the USA, for example, unable to conduct research using pluripotent stem cells, the UK should continue success in this area in bridging the gap between scientific research and commercialisation, with the role of regulators crucial in this process.

2.2.5 The use of 'Real world' evidence (RWE); the use of data generated in normal clinical practices, used in conjunction with data from randomised clinical trials, will become increasingly important in demonstrating the value of a new medicine. The MHRA should be able to define a national regulatory policy to allow RWE to be used to support registration. See also section 3.1.

Relatedly, consideration could be given to permit biopharmaceutical companies and research charities to access patient-level data in the Clinical Practice Research Database to facilitate clinical trial design and implementation.

2.2.6 The role of regulatory science; maintaining and expanding the role of regulatory affairs expertise is crucial for the development and approval of medicines. The MHRA needs to remain at the forefront of this development to strengthen the support provided to the UK's pharmaceutical industry. In particular the National Institute for Biological Standards and Control (NIBSC) should be able to further develop its global leadership in the field of biological medicines.

2.2.7 Training the world's emerging regulatory agencies; The MHRA is already frequently asked to provide training and to conduct inspections in countries that are developing their regulatory skills. The MHRA should be enabled to develop this example of leadership much further.

2.3 A key opportunity for the MHRA; The evolution of the Early Access to Medicines Scheme

In 2014, the Government established an 'early access to medicines scheme' (EAMS) which held the promise of new, ground-breaking medicines being made available to patients 'several years before licensing' (https://www.gov.uk/government/news/cutting-edge-drugs-to-be-fast-tracked-to-patients).

However, EAMS is allowed to exploit flexibilities that exist only within current EU regulatory legislation: the current scheme is not, therefore, as flexible as it could be in order to deliver the potential range of new treatments for patients, including drug/medical device combinations, cell therapies and genetic treatments. Extending EAMS to these treatments could see their use in the UK years before other countries in Europe.

The opportunity of such a system becomes even greater when considering the challenges that the licensing of technologies, that are just appearing on the horizon, pose to existing EU

medicines legislation. These include drug/medical device combinations, cell therapies and genetic treatments. A great deal of the scientific excellence to develop these treatments, which hold the potential to cure genetic diseases such as cystic fibrosis, is already here in the UK. There are therefore, obvious opportunities available to a UK regulator, able to operate in a simpler and more streamlined way.

Indeed, it is not an overstatement to say that the UK could have *cured* a large number of genetic disorders whilst the EU is still *treating* them.

There have been criticisms of EAMS from industry, including the fact that it is unfunded. So how could it be improved? While its initial "promising innovative medicine" (PIM) designation stage is both useful (e.g. to encourage investor confidence for SMEs) and relatively easy to navigate, the later "scientific opinion" stage of the current EAMS is direct cost and resource-intensive for companies. Also, the medicine is provided free by the pharmaceutical company until an opinion is provided by NICE which, if positive, should be the signal for NHS England to commission the medicine formally.

Reducing the timelines between regulatory approval, cost-effectiveness assessment by NICE and NHS commissioning is a primary objective of EAMS, but it is still too young a scheme to know if this will be the reality. A future scheme could be made to guarantee rapid adoption by the NHS, following a positive cost-effectiveness assessment, and be made more "enabling" in terms of its regulatory flexibilities earlier on, That is when a case could more justifiably be made for the company to provide the medicine without charge during the scheme. In this way, it would be a great example of how the public and private sectors could collaborate effectively to share risk and reward for patient benefit.

Additionally, the constraints of the current scheme arise because it simply exploits flexibilities for a national approval that exist within current EU regulatory legislation i.e. it is not "new" legislation. We need to be considering, therefore, the potential ability of the MHRA to design bespoke regulation for the UK. While it would be the MHRA's discretion to determine the detail of what this would look like, given its globally recognised status, it should be expected that where the MHRA leads, others in the world might follow.

So, what could this mean for patients? The scheme could incorporate new national regulation to cover, for example, the aforementioned areas of drug/device combinations, cell-based therapies and genetic treatments - the science-base for this already exists in the UK.

It could also incorporate the smarter use of real-world evidence to inform the regulatory approval of new treatments. Under existing legislation, the ability for UK regulators to make smart use of 'real-world evidence' – i.e. data that comes from sources other than randomised control trials – is heavily constrained. The European Medicines Agency is already exploring the use of real-world evidence in its 'adaptive pathways approach pilot' (http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000601.jsp), but this work has been criticised by other bodies in Europe – including the German health technology assessment body, IQWiG, which argued in August 2016 that it is

"high time to pause for a moment and rethink the whole concept" (http://www.pmlive.com/pharma_news/germanys_iqwig_perplexed_by_emas_adaptive_pathways_plan_1096728).

Ultimately for patients, it would mean their physicians would have the potential for "earlier approvals to use" a larger range of innovative treatments than exist today. It is "potential" because patients' ultimate access to them would also depend on them being assessed as cost-effective and then bought by the NHS! So, as with so many other opportunities we have, it would only become real if we work consistently as a single, joined-up, delivery system.

2.4 Towards a Status Quo, or something different?

The likelihood of an extended negotiation period means there may be little material change for at least two years and, perhaps, 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. Additionally, any key regulatory functions performed by them, including qualified or responsible persons and siting of databases.

If the UK chooses the EEA route, little will need to change, even after Brexit, as all EU rules will apply within the UK. This means UK companies would be 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. In addition, 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.

Were the UK to choose the Swiss route or WTO, much of UK life sciences law is derived from EU law either through Directives implemented nationally in the UK or through EU Regulations that 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.

A solution for some aspects of regulation might be a series of mutual recognition agreements in relation to both medicinal products and medical devices. Since UK governance in both sectors is widely respected throughout Europe, there is little reason (other than possibly political mischief making) why this could not be achievable. It would be particularly important for the continuity of the supply chain to ensure importers and manufacturers could 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.

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.

Negotiations are likely be drawn-out, challenging and uncertain, so it will be important for business not to take precipitous action since, 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.

Indeed, from conversations held recently with the MHRA leadership and statements from the MHRA website (https://www.gov.uk/government/news/medicines-and-healthcare-products-regulatory-agency-statement-on-the-outcome-of-the-eu-referendum), we are highly encouraged that it is "business as usual" for the MHRA in terms of its routine regulatory work. This will be at least for the short and mid-term future, 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 is also recognised and endorsed by its EU partners and EMA leadership.

2.4.1 Analysis

Technologies currently in research, particularly cell and gene editing therapies, will test existing regulatory approaches to the limit. For example, gene editing therapies will often be specific to humans – limiting the use of animal safety studies – and will target some of the rarest diseases where there are too few patients to conduct traditional clinical trials. The most advanced technologies in development will be designed – 'lego-like' – to treat individual patients, and clinical trials will be impossible to run in each case.

The most forward-looking regulators around the world, including the Food and Drug Administration in the United States, are already considering what impact these new technologies will have on their own regulatory approaches (https://www.healthra.org/download-resource/?resource-url=/wp-content/uploads/2016/06/Gene-Editing-Worshop-Summary.pdf).

Similarly, Japan's MHLW has introduced its own SAKIGAKE Designation System, designed to promote R&D in Japan by achieving early practical application for innovative pharmaceutical products, medical devices, and regenerative medicines (http://www.mhlw.go.jp/english/policy/health-medical/pharmaceuticals/140729-01.html).

Outside the pan-European medicines licensing system, UK regulators would be free to do likewise, possibly to include working more collaboratively with these leading regulators – increasing the attractiveness of the UK both as a location for research investment and as a place to launch new technologies first.

2.5 The key role of The Health Research Authority (HRA)

The HRA was established via clauses in the Care Act and works to protect and promote the interests of patients and the public in health and social care research. As such, it is a pivotal partner organisation of the MHRA. EMIG has worked to influence the HRA as another key player for the UK. Building on the successful overhaul of the research ethics committee service in the UK, it now has a broader agenda that encompasses a drive towards greater research transparency and the streamlining of NHS R&D approvals. The HRA has issued a 'business as usual' statement akin to that of the MHRA. In conversation, the HRA has indicated it will be working closely with the MHRA, NIHR and others to look at strategic priorities beyond its current focus on NHS Approvals. It recognises that its ambitions for UK-wide competitiveness, enhancing and sustaining the UK as a great place to do health research, will be in even sharper focus as a result of vote to leave the EU.

It is also worth noting here that the Care Act also gave duties to other organisations to ensure full co-operation with the HRA "in the exercise of their respective functions relating to health or social care research, with a view to co-ordinating and standardising practice relating to the regulation of such research". In addition to the MHRA, these included;

- the Secretary of State for Health;
- the Health and Social Care Information Centre;
- the Chief Medical Officer of the Department of Health;
- the Human Fertilisation and Embryology Authority;
- the Human Tissue Authority;
- the Care Quality Commission;
- the Administration of Radioactive Substances Advisory Committee;

It will be important that these duties are adhered to, reviewed and, if need be, strengthened in order to provide the HRA the leverage it needs to deliver the full benefit of its new service and functions.

3. UK Market Attractiveness

The UK represents some 3% of the world market for all medicines, but considerably more for innovative, costly treatments (IMS 2016). This may be surprising for even industry professionals who firmly believe the UK to be very slow in adopting innovative medicines.

As with most EU states, the UK continues to search for financial savings, so has rationed and sought cost reductions on most of these more expensive medicines and devices.

There is an apparent conflict between these two preceding statements and it may be partly explained by the fact that c. 60% of all National Institute for Health and Care Excellence (NICE) Guidance is now associated with a Patient Access Scheme (PAS).

NICE is a highly respected and influential health technology assessment body and the UK is widely used as a reference price state by 55% of major global markets, which includes many EU countries.

While a positive nod from NICE is recognised internationally, a NICE 'no' can have dire consequences, triggering other countries to negotiate downwards on price. These two factors create a synergy for the UK that benefits companies by enabling them to compromise on only 3% of their global business via a PAS, while positively impacting via reference pricing, on 55% of major global markets because their UK list price is protected.

Additionally, the MHRA has developed its own Early Access to Medicines Scheme (EAMs) (see section 2.3) for unlicensed medicines. The Department of Health (DH) is also due to publish its (delayed) review on accelerated access in response to the EU adaptive pathways initiative for early licensing.

There are also other facts that reinforce the global importance of the UK:

- The UK percentage 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;
- The UK is joint 3rd (with Germany) in the number of global HQs after the US and Japan;
- The UK is in the top 5 worldwide in terms of life sciences industry and R&D headcount;
- Importantly, the UK is widely acknowledged to be a global leader in health technology assessment (HTA) and in the emerging speciality of "data science" that enables the collection and analysis of real world evidence (RWE) to contribute to the evaluation of effectiveness. Such a focus requires joined up health informatics systems and the application of data science, a field in which the UK currently has a lead over the rest of the world. With a coordinated focus on medicines and patients, this is an advantage that, in the current situation, the UK should seek to exploit more assertively on an international basis (see addendum). A vision for real-world data use is proposed below.

Nevertheless, the place of the UK in new product launch sequences is already under a degree of scrutiny, although EU membership alone is not necessarily the most important factor in launch and investment decisions.

3.1 A vision for Real-World Data collection in the UK

The problem

- Current drug development paradigms are based on data from randomised controlled trials (RCTs). While these will always play a central role to define a medicine's efficacy and safety, they are not always either feasible e.g. in rare diseases with tiny patient populations or with the move towards more personalised treatments. Also, due to their tightly-controlled designs, they may not recruit study populations that are fully representative of how effective the drug will be in the total future population of patients that could be expected to be treated with it.

The solutions and opportunities

- Novel ways of doing trials are therefore required that are integrated with care systems rather than being separate from them. This would bring the possibility to increase efficiency by reducing time and costs, as well as provide data that are relevant to how the drug will be used in a "real-world" setting.
- The application of "Data Science" is a prerequisite and there are many UK-based opportunities to exploit it. Additionally, this can benefit from the large investments made by successive the UK governments in the infrastructure for health research.
- The opportunity to merge research with care to increase efficiency should be attractive to investors and improve patient access/care. As such, the healthcare system can become a risk-sharing partner with industry.
- The data would be widely applicable to many parts of certainly the western world due to genetic similarities in the populations.
- To support the earlier approval of selected innovative medicines, as is the EU mandate via the collection of data to inform licensing.
- This could be extended to lead the identification of opportunities for rapidly repurposing medicines.
- The UK has significant leadership in the EU data science arena. For example, through the "big data for better outcomes" IMI projects which are 'disease specific'. Depending on how negotiations proceed, the UK could capitalise on this funding by becoming the leading centre. Two of these projects are already being led by UK. They have a large number of UK academic partners and NICE coordinating all the EU policy input (Regulators, Payers and HTA). There is a significant opportunity for public-private partnerships to develop skills/methods. If UK takes the lead, we should win this investment.

The enablers

- The UK is strong on methodological research, which needs to be coupled with regulatory science becoming an established discipline.
- Specialist centres are being developed to improve patient care and we also have the nationwide network of AHSNs, with their core aim to improve patient outcomes by enhancing whole care pathways.
- The NHS patient number identifier, and the capabilities that can be exploited because if it, is unique in the EU system. For example, many different types of research study can be run using data from this system and, as such, it is the UK's jewel in the crown. However, it's not yet being capitalised on.
- Develop a "bespoke" integrated single process to evaluate rapidly the patient benefits of "high-potential medicines" (currently this is performed as a series of processes led by separate organisations).

3.2 The criticality of a NHS being receptive to industry

One critical factor is how the NHS is perceived by industry with regard to the adoption and diffusion of new medicines and health technologies. For a long time, this has been largely a negative view, compounded now by the increasing insistence of NHS Trusts for industry professionals to pay to be registered on a database to demonstrate they're "credentialed" to enter hospitals for discussions with healthcare professionals.

Some are interpreting this as further evidence that "the NHS is not interested in our business". Unless this "sledgehammer" approach is ameliorated in some way, it would not be surprising if some companies chose to withdraw their people and products from the UK in their entirety, let alone decide there are alternative places in the world to place their research investments.

Following Pfizer's decision in early 2011 to close the large part of its enormous R&D facility at Sandwich in Kent, it was no coincidence that the Government produced the "Life Sciences Strategy":

(https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/32457/11-1429-strategy-for-uk-life-sciences.pdf) and "Innovation Health and Wealth"(IHW) (http://webarchive.nationalarchives.gov.uk/20130107105354/http:/www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/documents/digitalasset/dh_134597.pdf) later that year.

A key aim of IHW was to accelerate the adoption and diffusion of new medicines and health technologies that could be shown to enhance patient outcomes, deliver value to the NHS and create wealth.

Fifteen regional "Academic Health Science Networks" were established as the key delivery vehicles for this. These were licensed in the autumn of 2013 and are beginning to show their effectiveness (http://www.ahsnnetwork.com/wp-content/uploads/2014/12/AHSN-Impact-Report-2016.pdf) e.g.:

- **£20 million support** for businesses through the SBRI Healthcare programme
- More than **800 jobs** created or safeguarded
- Supporting **7 test bed sites**, which link industry into the NHS and improve outcomes
- for citizens
- Supported over **500 new products or services** to be co-developed and/or supported into the NHS

AHSNs also have direct regional "honest broker" access to many NHS and academic organisations, which include universities, Public Health England, Health Education England, CLAHRCs, Clinical Networks, Clinical Research Networks, Commissioners, Providers, Van-guards and those responsible for the Sustainability & Transformation Plans. The potential, therefore, is enormous for AHSNs to do much more regarding health technology adoption in the pursuit of better health outcomes.

Yet, with their initial 5-year licence period ending in 2018, AHSNs are now beginning to be notified by NHS England of the relicensing process or, more likely, what will be a full public tendering/procurement process. We would suggest that such a protracted and disruptive process is the very last thing that's needed at this time of uncertainty and that, given AHSNs are doing good works, a more "light touch" relicensing process is instituted now. This could of course be reviewed in a few years' time, once the dust has settled on current economic jitters and additional data have been gathered on AHSNs' collective performance.

3.3 Parallel Trade

The principle of free movement of goods enables someone other than the patent holder – typically a distributor – to acquire a product legally marketed in one member state of the EU and sell it in another, without the consent of the company originally marketing the product.

This is the essence of parallel trade and provides an opportunity for parallel traders to legally purchase products in markets, where the regulated prices are low, and sell them in higher priced markets, profiting from the transaction.

The trade is regulated, in that all traders have to be registered as pharmaceutical wholesalers, are subject to the same regulatory regime as all other pharmaceutical wholesalers and must be licensed to import each product into their destination market. Indeed the major international pharmaceutical wholesalers include parallel trade as part of their business.

The scale of parallel trade is difficult to measure, as there is no comprehensive dataset, but it is clear that in some markets, and for some products, it is substantial. Information available from IMS Health suggests that, in terms of overall parallel imports, the UK is second only to Germany in volume and that in 2013 parallel imports amounted to €784m (£648m at than exchange rates):

https://www.imshealth.com/files/web/Germany/Publikationen/ReportsWhitepapers/Parallel-trade-with-drugs-Whitepaper-IMSHealth-042015.pdf

The UK is not only an importer of parallel traded products. In some cases UK prices are lower than some other European markets and products are parallel exported, especially to Germany.

The impact of parallel trade is mixed. Parallel trade is clearly detrimental to the pharmaceutical industry. Manufacturers incur a loss in profitability equivalent to the price difference between export country and destination country, at list prices multiplied by the sales volume of the parallel imported product. This loss to the industry is redistributed predominantly among retail pharmacies and parallel distributors.

The industry view is that this results in a reduction in investment in R&D for the introduction of new medicines. While it is not possible to draw a direct connection between the profits lost through parallel trade and expenditure on R&D, clearly the profits foregone must have some impact. It should be noted that the industry incurs this reduction in potential revenue whichever the direction of trade – whether profit foregone through the import of products from lower priced markets or the profit foregone by the export of products to markets where a higher price would otherwise have been charged.

Since the UK is one of the leading markets for both parallel imports and parallel exports, this is not a trivial factor for the international pharmaceutical industry.

It has also been argued that parallel trade may put patients at risk, for two reasons. The extended distribution chain, which may involve not just transportation but also repackaging, over-labelling and translation of patient information leaflets, provides increased opportunity for errors and omissions. At the very least it increases the difficulty of effective regulatory supervision. Secondly, the extended distribution chain may provide the opportunity for counterfeit medicines to enter the supply chain, putting patients at risk. There have been isolated examples of this in the past, but none have been documented recently.

3.3.1 The future of Parallel Trade

In the short term, parallel trade into and out of the UK will mainly be influenced by the value of the £ versus the €. However, the future in the longer term is dependent on the nature of the trading relationships established on leaving the EU.

If no alternative is negotiated following exit from the EU, parallel trade between the UK and EU member states (and members of the EEA) will cease to exist. Should the UK choose to remain in the EEA, there would be no change to parallel trade. Other options, such as membership of EFTA or application of World Trade Organisation rules, would prohibit parallel trade unless there were specific agreements to allow it.

3.4 Time for a novel approach to funding new medicines

In addition to promoting actively the role of the AHSNs, the industry also needs to prevail on 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. An opportunity could be the next Pharmaceutical Price Regulation Scheme (PPRS). The current PPRS will expire at the end of 2018 but the negotiations for the next Scheme are likely to start in early 2017. Two of the great failings of the current Scheme are:

1. The pharmaceutical industry will pay c. £3 billion in rebates to the Department of Health (DH) over the course of the current five-year Scheme. The purpose of these rebates is to fund the uptake of innovative new medicines launched since the beginning of the scheme in January 2014. In previous Schemes, the industry agreed to significant list price cuts and NHS prescribers felt the direct benefit to their budgets.

   However, the rebates are paid to the DH and there is little transparency on how these rebates are 'passed' to the NHS. In Scotland and Wales, Innovative Medicine Funds have been set up by the Devolved Nations. The £90m Fund in Scotland, if pro rated across the UK, would become a £1 billion New Medicines Fund. England needs a discrete New Medicines Fund, separate from other NHS budgets and funded by industry rebates.

2. The removal of the 'taper'. Understanding the background of the 'taper' will be helpful. Companies with annual sales to the NHS below £5m are exempt from the PPRS rebates. The taper is where this £5m exemption was also applied to companies with annual sales to the NHS of up to £25m – so companies with sales to the NHS of up to £25m could claim exemption for the first £5m of their sales. In the 2005 PPRS, the taper was £1m and applied to companies with annual sales up to £5m.

   EMIG has long pressed for the taper to be increased and, in the 2009 PPRS settlement, the taper was increased to £5m and applied to companies with annual sales up to £25m. The cost of the taper at that point was £75m for the full five years of the Scheme (DH Letter from Earl Howe).

   In preparation for the 2014 Scheme, EMIG lobbied to have the taper raised to £10m and applied to companies with annual sales to the NHS of up to £40m. The 'taper' needs to be restored at this new level.

The PPRS also does not allow for novel payment models. These are widely advocated and companies are keen to explore them. The forthcoming renegotiation of the PPRS therefore presents an opportunity to do this. NICE is already showing leadership in this regard under the adaptive pathways project ADAPT SMART. Here, payers and industry representatives have agreed some pilot proposals for novel reimbursement strategies that can be taken forward for further exploration. However, additional resources are needed for NICE to optimise its work here and to do it at a UK level.

Finally, in this section, it should be noted that the Life Sciences Minister role has been lost at a critical time for the industry. The Government needs to develop a proper and comprehensive industrial strategy for the life sciences and to have a dedicated champion to deliver it. This would send a needed message to a currently puzzled world audience that the UK Government is serious about the life sciences, in all its guises, remaining as a core scientific and commercial ecosystem for the country and to develop its presence further on the global stage e.g. in conjunction with the work of the new Secretary of State for International Trade.

We therefore urge the Prime Minister to clarify the Government's future support for the life sciences as a matter of urgency.

4. Fiscal and Trade matters

4.1 Impact on taxation

The implications for the future framework for Customs Duty will be of most significance but the impact on VAT and, to some extent, Corporation Tax will also be of importance. Not every aspect of UK and international taxation that could be affected, are covered, but this section draws out those considered of greatest significance for Life Sciences.

4.2 Customs Duty

There are a number of existing models that could be adopted to shape the UK's trading relationships but none are likely to be optimal. The UK is currently a member of the World Trade Organisation ('WTO') as a consequence of its membership via the EU. This will need to be renegotiated, as will new Free Trade Agreements with EU members and rest of the world. Upon leaving the EU, the UK Government can determine its own duty rates applicable to imported goods and they could vary from those currently in force as set by the EU. For the industry, the primary concern will be that duty does not increase.

Other implications include:

- A custom border will be created between the UK and the EU that may have an effect on delivery times and additional requirements to submit import and export declarations. As a result, the documentation and paperwork for trading with the EU will change and it will be important to ensure that this does not become burden-some. There is concern over the ability to implement this effectively in a short timeframe.

- The need to retain the current 0% duty rates for pharmaceutical products, and potentially extending this to include products commonly imported by the industry which are not currently given duty free treatment by the EU such as API at 6.5%.

- The implementation of new and additional administration for export controls and licensing.

- The continuation of duty reliefs (e.g. imports for Clinical Testing and inward processing relief) currently provided for under EU law.

4.3 VAT

UK VAT is based on the EU VAT Directives, implemented under the Value Added Tax Act 1994. Unless the UK Government decides to abandon the key VAT principles, the impact of a UK exit is likely to be limited to domestic transactions, but there may a significant impact on cross border trading. In the short term, it would appear that maintaining the VAT system as it is currently operated would be the preferred outcome. Systems changes to adapt to new VAT principles can be very costly as well as the increased risk of error. On the other hand, companies should no longer need to file intra EU trade declarations such as Intrastat declarations and EC Sales Lists; such declarations will be replaced by customs declarations for goods entering and leaving the UK.

4.4 Cashflow

As a general rule, VAT is not a cost within this sector. Nevertheless, once the UK exits the EU, import VAT will be payable on all non-UK sourced products before they can be brought into free circulation within the UK (subject to having a deferment account). This approach is likely to have a cashflow cost for almost all taxpayers. If not addressed, it could have a material impact on working capital.

4.5 Reduced rates

The UK Government will have more freedom to decide whether it wishes to apply new reduced rates to goods and services. At present, any change in UK VAT law that is contrary to existing EU VAT Directives and or EU case law, must be approved by all 27 members of the EU. This limitation has most recently been illustrated by the proposed reduction in the VAT rate to 0% for sanitary protection, which has been on the UK's agenda since 2000.

4.6 VAT and healthcare

VAT is charged on sales of product to the NHS, private hospitals and individuals and cannot be recovered. **Leaving the EU may provide an opportunity to engage with the UK Government to discuss the application of reduced rates to certain pharmaceutical products and thereby reduce the cost of healthcare in the UK.**

4.7 Corporation Tax

Leaving the EU may have limited impact on corporation tax as the UK has discretion over setting its own corporation tax policy and more recent changes have been driven predominantly by the OECD's BEPS project. The current Government appears to remain

committed to ensure the UK has a low corporation tax rate in order to maintain the most competitive tax system in the G20.

4.8 R&D relief and Patent Box

Major changes will be unlikely, but if the UK does not become a member of the EEA, consideration should be given as to whether the restrictions on R&D tax credits for SMEs, as a consequence of State Aid, could be alleviated. This could include increasing the headline SME R&D tax credit rate from 33%, removing the €7.5m project cap on R&D relief for SMEs and removing the restriction on grant funding which itself is a notified State Aid.

The Patent Box is only narrowly impacted by EU law. Nevertheless, with the reducing headline corporation tax rate the relative benefit of the patent box is diminishing. This would therefore provide opportune timing to lobby for a reduction in the patent box rate.

4.9 EU Directives

There should be no direct impact on the EU Directives that have already been incorporated into the domestic UK tax legislation, but the Government may choose to retain or remove them. Outside domestic legislation, the Parent Subsidiary Directive is perhaps the one that business would most need to be preserved. After an EU exit, the cost to a UK company of investing via a subsidiary in other Member States would be higher where the UK's double tax treaties do not reduce the withholding tax on dividends paid to the UK to 0% (e.g. Germany and Italy).

4.10 Double tax treaties

With Brexit, UK's ability to compete effectively in international trade becomes ever more important. Certain treaties will need to be addressed as a consequence of leaving the EU to avoid the increased incidence of double taxation for UK companies. Furthermore, it is hoped that Government would use this impetus to improve terms in a number of other key treaties.

5. Legal, Intellectual Property (IP) and Employment matters

5.1 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.

5.2 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.

5.3 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, as well as member state pricing and reimbursement approvals, may need to be examined. When entering into new contracts, it should be also considered whether to include a specific provision dealing with the consequences of UK departure.

Since 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.

5.4 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 the Department for Exiting the EU (DEXEU), 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 might 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.

6. Research and Development

6.1 Universities and 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.

Valuable research grants are awarded by the European Research Council, an EU initiative. Notably Horizon 20/20 is committing some €80 billion of funding available over 7 years (2014 to 2020). EU membership is, however, not a condition of eligibility under this fund and Switzerland as an EFTA member has benefitted in the past. Moreover, it might be argued that the potential relief from EU contributions should make more money available for the direct UK funding of R&D. Let's look at the figures:

- We currently pay a net figure of £8.5 billion per year to the EU;
    - **https://fullfact.org/europe/our-eu-membership-fee-55-million/**

- The Horizon 2020 budget totals 80 billion Euros over 7 years = 11.4 billion Euros per year = c. £9.1 billion per year.

- The current Medical Research Council (MRC) budget is £580M.

- The current Innovate UK budget is £547M.

So, purely as an illustration, if circa 15% of the amount paid annually to the EU were to be diverted to two of the key organisations of relevance to the life sciences sector, their budgets would be doubled and significantly increase their ability to enhance biomedical science and businesses. This could include a significant funding increase for the very successful Biomedical Catalyst that is jointly run by the two organisations. In essence, therefore, it should be possible to create an evolved form of a peer-reviewed, call-based, "biomedical research accelerator initiative", where applications are led by UK-*based* (i.e. not necessarily a UK national) scientists and businesses.

6.1.1 Collaborations; Another area could be to take a refreshed look at academia/industry collaborations. There is a large appetite within the life sciences industry to engage more with our universities, if they can do so in a manner that is 1) fast 2) harnesses simply the best science available in *multiple universities* for a single project and 3) is based on a mutual agreement about shared risk-shared reward.

In his excellent report of 2012, "A Review of Business-University Collaboration" (https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/32383/12-610-wilson-review-business-university-collaboration.pdf , Sir Tim Wilson cited the importance of universities working for "collaborative advantage". His words then, are even more pertinent now;

"Many would argue that competition within the UK university sector has driven efficiency, effectiveness and diversity over the last two decades whilst maintaining excellence. No one university covers the entire landscape of university business collaboration, and yet each domain is important to the businesses that rely upon it for their development. Diversity is a strength of our university sector in that it enables specialisation in strengths; it ensures that the entire spectrum of business support can be found somewhere within the university system.

Whilst it is the role of university leaders to promote the excellence of their own universities, our university sector as a whole is a key asset in the economic future of our country. The efforts of UUK to promote these strengths are admirable and regional associations, where they exist, attempt to present a complementary profile of university missions. It would be helpful if university leaders could emphasise the complementary strengths of UK universities in terms of meeting business needs. ***Without mutual recognition of the expertise of others, the competitiveness of UK universities has the potential to become a weakness****.*

Specifically, in terms of the reputation of the sector as a whole, it is critically important that universities are open about the domains in which they operate and refer demands that they

cannot meet to another university or a source of guidance where such information may be found. Collaboration between universities in supplying business needs can only benefit the university sector as a whole. Universities may wish to reflect upon the concepts of collaborative advantage in meeting business needs and review their policies on the referral of business enquiries to other universities or relevant agencies".

For example, were the South Eastern AHSCs (i.e. the universities and their associated NHS Trusts) of Cambridge, Imperial College, King's College, Oxford and University College be incentivised to present industry with a single unified modus operandi for collaboration, they could rightly become the best and most influential biomedical cluster in the world. Who would not then want to come and work with them? The world-class universities in the north of England and Scotland and their associated NHS Trusts, have a similar opportunity. All that is required is the right incentive and their collective will to make it so.

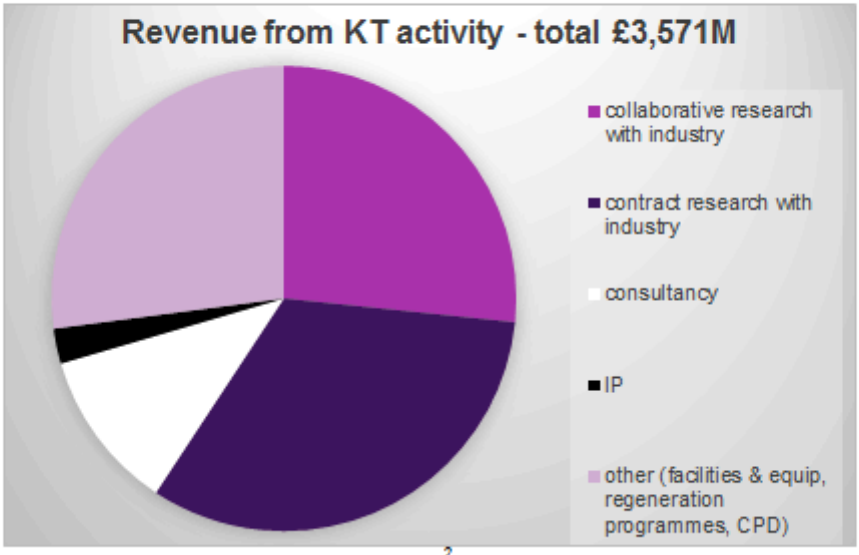
There can be no escape from the fact that "funding" will always be an incentive and, as such, the influence of the Research Excellence Framework (REF) is key. The recently-published "Stern Report" (https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/541338/ind-16-9-ref-stern-review.pdf) recognises that the REF is not currently designed to reward interdisciplinary collaborative research performed by an institution and has proposed the following recommendation;

Recommendation 5: Institutions should be given more flexibility to showcase their interdisciplinary and collaborative impacts by submitting 'institutional' level impact case studies, part of a new institutional level assessment.

However, the issue of the need to incentivise more than one university working together in a multidisciplinary way on a single project e.g. with a single commercial partner, has not been addressed. We therefore, recommend that this possibility is explored as a high priority.

6.1.2 IP; Another area that would make a big difference to enable easier engagement with industry, would be for universities to become more open in their approach to IP arrangements. This is often a cause of major delay and frustration during the contracting process, and it is unnecessary for two main reasons. Firstly, it is not common for significant IP to arise from such research. Secondly, the amount of income that universities derive from IP is miniscule compared to that from other sources;

Revenue from KT activity – UK HEIs



Source: HEBCIS 2012/13

6.2 Translational Drug Development

The UK has the potential to take a leadership position in this area, i.e. the translation of lead candidate molecules from pre-clinical studies to early-phase clinical studies, which will attract substantial inward investment. We have many strengths to bring to bear (summarised below) but need to overcome two primary obstacles: 1) **the World does not know of our capabilities and 2) we are not joined up as an industry.**

Key capabilities which will help to achieve leadership include:

- A world-leading academic research base with KOLs in most therapeutic areas
- a service sector that can provide all the technologies and expertise required for translational drug development, including pre-clinical and clinical testing, bio-medical imaging, and manufacturing development
- access to patients through the NIHR/NHS and patient advocate groups
- specialist expertise and focus in developing technologies, such as cell and gene therapy, immune-oncology etc.
- expertise in important therapeutic areas, such as dementia
- an attractive fiscal environment, e.g. R&D tax credits, the Patent box
- the potential to create a supportive regulatory regime by re-assessing, for example, the EU Clinical Trials Directive

A prerequisite for gaining full value of the various capabilities is to ensure all activities are joined up and aligned, perhaps establishing a concept of TransMed UK. In addition, we need

to develop a clear set of messages that can be clearly marketed by the new Department for International Trade (DIT) and governmental organisations.

6.3 The importance of the organisational Operating Model as a vehicle for science delivery

It was mentioned earlier that there is a large appetite in the life sciences industries for greater engagement with academic basic and clinical science in the UK, as long as the arrangements for that engagement can be made with maximum speed and efficiency. The UK science base is truly world-class in so much of its content. But that loses relevance if it takes "forever" to establish the contractual grounds for a collaboration. So, the physical operating model for access and engagement is, critically, just as important as the science itself.

Some of the factors that would help achieve an optimal operating model, either for groups of universities and their associated NHS trusts, or for a single large organisation such as, for example, The Francis Crick Institute, have been noted above. To these should be added factors, such as;

- A central, "front of house" office should be put in place which has the authority to act in front of its "customers" on behalf of its members.
- It must be able to show how it adds value e.g. be able to prosecute the contract development process faster than the company would simply by engaging with a single university alone e.g.;
- Some universities can have a reputation for usually seeking a "win, with little risk" for themselves. The industry would look very favourably however, on a university, or cluster thereof, taking a refreshed stance towards what would constitute a more open, "shared risk and shared reward" arrangement.
- Co-ordination & harmonization of the various clinical trial services offered by the members
- Visibility of the drug discovery and development pipelines
- A conduit to access expertise in therapeutic areas/technologies e.g. consultancy services
- Access to techniques and capabilities for drug development across the members (imaging, -omics, anti-body engineering etc.)
- A show case for academic capability and expertise
- Standardisation of interactions (contracts and operating procedures etc) between members and a commercial partner. These already exist in a form in some research programmes e.g. the Translational Research Partnerships run by NOCRI. These could be refreshed with a view to their wider use.

Examples of these "concierge", single portal access offices already exist, at least in principle, e.g. within MedCity and The Northern Health Sciences Alliance (NHSA). However, we encourage the critical focus on the operating model for delivery of the science to be placed more centre-stage.

6.4 Clinical Research in the NHS

In terms of the key factors of "time, cost, reliability and quality" that industry uses to decide where to place its clinical research, the UK has made great strides in recent years to ensure it remains competitive on a world stage. For example, the depth and breadth of world-class clinical science supported via the NIHR in England is enormous. It has pioneered successful new models of industry/academia/NHS collaboration such as the Translational Research Partnerships programme, and put in place several organisational measures to help industry navigate what is undoubtedly a complex environment.

The HRA's (see earlier) new single "HRA Approval" will avoid the need for sponsors to obtain an individual R&D approval for each NHS Trust where it plans to conduct clinical research.

But, areas for performance improvement remain, and arguably these largely reside in areas outside of either the NIHR's or the HRA's direct remit. The key issue is one of wide variation in performance across NHS Trusts, both within the R&D Office function and at the research clinic level. While a root cause of this is undoubtedly because Trusts are often under-resourced to do clinical research, their organisational independence is also a confounder.

This leads to a lack of harmonisation with regard to performance standards. As such, and similar to the call for universities to work for collaborative advantage, there is a need for research-active NHS Trusts to agree;

- An approach for the provision of full transparency on costs and overheads.
- A target timeline for contractual review and agreement.
- An approach for how study feasibility might match actual recruitment more frequently, especially to avoid over-promising where there are known stretched resources.
- A plan to ensure better trained and greater stability and consistency of site study teams.

6.5 The role of research charities in R&D

From Eric Low, CEO of Myeloma UK;

The UK's medical research charities play an increasingly important role to make the country an attractive place to invest. The members of the Association of Medical Research Charities (AMRC) fund £1.6bn worth of research per year and increasingly in a more strategic way involving commercial collaborations. For example, Myeloma UK has a number of such collaborations with more in the pipeline. Leaving the EU does not *per se* cause that charity undue concern. Its most recent 'hybrid' trial involves about £8m worth of free drug to the NHS and about £3m in funding to its Clinical Trial Network (CTN). It could have up to 4 – 5 similar trials running simultaneously in the CTN. Part of the attractiveness of working with medical research charities in the UK who are NIHR partners is their ability to leverage NHS

research costs more or less for free. This is allows charities to do strategic evidence development in collaboration with industry to help support regulatory or HTA submissions.

This is unique and, as such, is a clear USP for the UK. Notwithstanding all the legal and policy issues, if articulated properly, the UK could be and should be the best place to invest. Myeloma UK also believes that the EU will want to keep many of the UK's key EU facing/relevant institutions close e.g. the MHRA. As such, it believes that new structures will be put in place beyond the current EEA and EFTA, because the UK's relationship with the EU and what it is has to offer is much more than Norway or Iceland, for example.

7. Skills and Training

Let's assume post-Brexit there is an absolute political will to make a success of such a dramatically different landscape. One of the main challenges to UK Biopharma firms will be the continued appeal to investors, and this is very often secured around the skills, talents and availability of the best people. Large corporates rarely struggle to secure visas for key people. Smaller, agile and talented start-ups however, lack resources and are therefore in danger of their businesses being stifled through reduced access to talent. Vacancies in the Biotech space to date in 2016 have increased by 21% in the UK compared to 1% across the rest of the EU. In addition to the growth seen in general vacancies within the life science space, the extensive consolidation and increasing numbers of large pharma now looking to rebuild their clinical teams could lead to further crisis, or, as explained below*, the possibility for a UK opportunity.*

The cost of staff has escalated in the last 15 years leading to increased costs for R&D. This has been fuelled by a continuing trend to outsource trials. Neither CROs nor large pharma have invested in the development of the skills required to fill the many roles created. However, there has been innovation in unusual quarters around the developing, funding and continued development of these much-needed skilled staff. Clinical Professionals, a pan- European staffing business, in 2015 launched a training programme that funded the training, development and placement of UK life science graduates.

Once *in situ* a team of trainers continued CIPD with each placed graduate in collaboration with the Science Council around an industry specific competency framework. Having now funded and placed multiple graduates in both SME and global pharma, their programmes have now extended to a pilot within the NIHR for Clinical Research Associates.

Now Clinical Professionals, in collaboration with Bart's Healthcare are funding science graduates to go through a two-week programme on Aseptic Techniques and Operations. This course opens a gateway for life science graduates to their first industry role. The unique relationship between Bart's Healthcare and Clinical Professionals allows CIPD to occur post placement whilst utilising the services of the staffing business to identify roles in industry.

In September 2016 a new fully-funded programme "CTA to CRA" will be launched by Clinical Professionals and will work in collaboration with London based academic institutes to allow

the newly trained attendees access to co-monitoring post-training to ensure their transition into new roles is as robust and industry relevant as possible. CIPD for 12 months post training in collaboration with employers will also ensure the skills and support is consistent. With large pharma now looking to rebuild their clinical teams, programmes such as this allow a new highly trained and supported network of newly skilled individuals to enter industry in a cost effective manner with no compromise on skill or development quality.

Each programme available is written and developed to be highly scalable, industry-relevant and cost-effective. As salaries can account for c. 75% of clinical drug development costs, stabilising these costs alongside the creation of supply of highly skilled staff offers the UK a fairly unique position in terms of its global competitiveness. Companies will always invest in countries that offer highly skilled cost-effective staffing solutions. Whilst Ireland as an example has succeeded in offering a home to many US Biotechs, the seams are already fraying around finding the staff required to fill these roles. The UK, with a range of highly skilled staff and novel development programmes for the supply of new highly qualified people, could ensure it remains an attractive destination for investment.

8. Marketing the UK

Clearly, none of the opportunities described in this paper will be realised optimally without effective global marketing of the UK. The new Department for International Trade (DIT), which replaced UKTI, has a golden opportunity, if not an imperative, to work with industry in a different way. Fundamentally, there is a need for it to recognise the advantages of working closely with UK biopharma, its trade associations and supporting organisations e.g. the staffing company described above to secure FDI. Sadly, UKTI did not fully do this, unlike its counterparts in other countries e.g. IDA Ireland. For example, just think how much knowledge experienced UK staffing organisations have of the US biotech start-up space, that could be exploited to national advantage?

Ultimately, were DIT to engage in a greater manner directly with the UK commercial life sciences sector, a robust message could be sent to show how the UK is still open for business, albeit in a different and potentially enhanced form. By engaging *collectively* with global biopharma start-ups at an earlier stage, prior to their decisions on where to locate in the EU, we have the opportunity to deliver the right type and level of information to encourage UK investment.

This could continue once a UK presence/FDI has been established. For example, EMIG has a ready cadre of highly experienced business leaders (CEOs, MDs, General Managers) who have expressed their willingness to act as business mentors to their counterparts in newly arrived companies. Simply having an experienced colleague in another company to act as a sounding board for all the "*in the UK, how do I do x, y, z*" questions could be of enormous benefit to help these new companies settle, and of course would send the right note of welcome. This is a completely free service offer that we urge DIT to explore further with us.

It will also be key for DIT to be staffed with commercially experienced and focused individuals. This could be achieved via a mix of permanent staff (to provide institutional learning and memory) drawn from the commercial sector, together with a dynamic on-going industry secondment programme. There is also merit in considering all or part of the new DIT becoming an "arm's length from government"/semi-state body to encourage a more entrepreneurial culture with a level of operational freedom that would not be seen in other government departments.

9. 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 on 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 camping to achieve its aims for healthcare and patients. Opportunities include:

- ensuring that the negotiation of any mutual recognition agreements affecting the life sciences sector are prioritised
- enabling the MHRA and NIBSC to exploit further its existing leadership in regulatory science and policy matters for a range of advanced product areas
- stressing the UK's leading role with NCEs and speciality medicines, the global influence of NICE determinations and the importance of international reference pricing
- working with NICE, the MHRA and Government to leverage internationally UK experience with real world evidence and the application of data science
- establishing a new medicines fund for the NHS from the rebates paid by the industry to the Government
- re-establishing the taper for small companies to encourage growth and investment
- streamlining and promoting the critical role of AHSNs
- using a proportion of the EU "rebates" to establish a "biomedical research accelerator" fund
- reviewing the nature of industry-business, and *critically*, university-university collaborations
- establishing the UK as the world-leader for translational drug development
- encouraging NHS trusts to harmonise their clinical trial performance operations and standards
- encouraging a positive policy for the easy movement of EU life sciences workers and generally protecting the UK science base
- exploring novel ways to develop skills and talent
- seeking a significant reduction in corporation tax as an incentive to inward investment
- asking the Government further to 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
- seeking the adoption of regulatory and reimbursement regimes designed to encourage rather than deter the use and adoption of new treatments
- partnering holistically with DIT to market the UK globally.

An important factor will be how well the industry can work with the MHRA and NICE in a common cause. Achieving such objectives could, in the medium term, more than outweigh any detriments of leaving the EU in attracting life sciences investment. Equally important will be the need for the UK's whole life sciences and healthcare community to work with industry in a consistently joined-up manner. This hasn't happened to date. Thereafter, the UK's holistic life sciences offering to the world has got to be assertively marketed and sold.

Critically, in a 'total Brexit' scenario, where the UK is not bound by EU medicines legislation, there will be a very real opportunity to go much further than the current system allows. Indeed, it is a valid assumption to make that – in a future and more liberal regime that could be developed in the UK outside of the EU – regulators here in the UK could approve the latest technologies and treatments for use in patients years before other EU countries.

A great deal of the scientific excellence to develop these treatments, which hold the potential to cure genetic diseases such as cystic fibrosis, is already here in the UK. There are, therefore, obvious opportunities available to a UK regulator able to operate in a simpler and more streamlined way. Indeed, it is not an overstatement to say that the UK could have cured a large number of genetic disorders whilst the EU is still treating them.

Finally, we suggest a vision for the future that pulls together many of the above opportunities into a single, fully integrated, health sciences ecosystem. In effect, this would establish the UK as the world's **"Open Centre for Health Sciences"**. This would feature a truly collaborative network of universities and their associated NHS Trusts working with the life sciences industry across the entire "bench to bedside and back" spectrum for the discovery, development, adoption and diffusion of medicines and medical technologies. The AHSN network in England and their equivalents in the devolved nations, MedCity, and the NHSA would all play a central, pivotal brokerage role, with the MHRA, NICE and HRA additionally involved as critical partners on each medicine's/medtech's journey.

To enable this, the absolute key issue is easy access to the best-skilled people, no matter where in the world they originate. We therefore, cannot overstate the urgency for the Government to explain how they will attract Biopharma to the UK to invest in order to deliver a healthier global future for us all and within this, how the UK will remain fully welcoming to the overseas scientific and business talent that contributes so significantly to our life sciences ecosystem.

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About EMIG

EMIG is the biopharmaceutical trade association that is the voice of 250+ companies and organisations, mostly SMEs, based in the UK. It represents a wide range of members from start-ups, whose prime focus is often research and development, to highly developed businesses delivering essential products to patients and the NHS. Indeed, EMIG members provide about 40-50% of all branded medicines, by volume, supplied to the NHS. Importantly, approximately 90% of its biopharma members are represented only by EMIG at trade body level. In addition to biopharmaceutical companies and their associated commercial service providers, EMIG also has patient groups, research charities, and universities in its membership, and their membership is free of charge. This enables EMIG to represent the views of our pharma members but balance these with views from a wider stakeholder group, including the interests of patients and the NHS. We therefore strive to adopt a more independent and holistic approach to policy matters. This rich blend also facilitates knowledge, understanding and information exchange between a diverse range of organisations involved in the life sciences that, without this as an enabling platform, might not otherwise occur.

ADDENDUM

Data Science for Better Therapies

Opportunities for New Research and Decision-Making Paradigms

Meeting Report, July 2016

Executive Summary Report reproduced with permission from Professor Sarah Garner of the National Institute for Health and Care Excellence (NICE)

Executive Summary

Leading academic researchers working in health data science, clinicians, industry leaders and representatives from research funders and regulatory bodies met in February 2016 at Manchester Science Partnership's CityLab to discuss current and future capabilities in data science research in the UK. They shared their experience in the field, reviewed opportunities and challenges for the UK healthcare system and agreed measures to help overcome current barriers and build on the expertise and data resources in the UK, enabling it to become a leading site for data science and health research using real world data in the future.

Several initiatives, such as the European Medicines Agency's Medicines Adaptive Pathways to Patients (MAPPS) project and the Accelerated Access Review in the UK, among many others, are currently underway and are driving the need to consider how best to use real world data in healthcare decision making. A wide range of projects involving the use and analysis of real world data for health and medical research are taking place in the UK but there have previously been few opportunities for key policy stakeholders and researchers in data science to share their experience and build together on existing expertise.

Key objectives of the meeting were to:

- Explore the current challenges in data science and the factors limiting developments and future progress in the field.
- Share ideas of best strategies to move forward, identifying concrete measures that will support the UK in becoming a global leader in health data science research.

The current challenges for UK's healthcare data science research were identified as:

Lack of strategies for bringing data together, with many different data collection systems managed by different organisations.

Researchers working in separate 'silos' and not collaborating effectively together or exchanging data, ideas and findings.

Shortage of data science skills. There are currently not enough people are being trained to use, process and analyse data and there is also a lack of further training for people working in the field.

Lack of communication and clarity from regulators, HTA agencies and payers on what is required from research and submission packages using real world data.

Lack of public and patient engagement in sharing their data collecting by the NHS and other organisations and using it for research.

Lack of funding for research using routinely collected data and reticence by journals to publish studies using this type of data.

Meeting participants reported a lack of support from research funders for translational research using real world data and studies bridging clinical practice and research and difficulties in getting these types of studies published in high impact journals.

The experts recommended the following measures to advance UK's capability for data science research in healthcare:

Theme 1: Build a collaborative environment

Improve collaborative working by developing networks of people across different sectors with an interest in a specific data area – academia, clinical medicine, industry and regulators – and enabling them to work together. The right incentives should be put in place, at both political and institutional levels, for people to work together and share research.

Establish ways to share data and expertise, such as with an e-Lab that enables sharing of information and knowledge to overcome the current lack of strategies for bringing data together and many different data collection systems. Technology, governance systems and incentives are required to bring data together and the group considered it important to *optimise the interoperability of technology systems, linking systems together* to get the most from them.

Encourage patient and public engagement and participation in sharing data for research. Meeting participants considered it essential to show people the benefits of sharing and re-using routinely collected data in research and in improving care. Initiatives should be set up to empower patients to share their data and engage them in research. This should include reporting back to patients on the findings of studies in which they have been involved so they can understand the value of sharing their data. Stories should be built on using data to

improve health and the difference this can achieve and case studies and examples should be shared.

Theme 2: Develop infrastructure, frameworks and knowledge

Establish funding mechanisms and support for research using routinely collected data. The group considered it was important to engage funders and help them understand the value of this type of research and recognise that research design and analysis will be different to traditional research studies and clinical trials.

Develop training and skills in data science, with top priorities being mathematical and computational skills, including bioinformatics, statistics, data mining, health informatics, health economics and outcomes research. As users of the data, the public and clinical sectors should also be targeted.

Agree best research practice guidelines for studies using real world data, including an ethics framework that may include technology to achieve dynamic consent and measures to achieve differential privacy, as appropriate.

Involve regulators, HTA agencies and payers in clarifying data requirements. Meeting participants suggested agencies should better communicate the data they will accept for regulatory approval and technology appraisals. They considered it important that researchers are able to dialogue with these decision makers around research programmes and data being used. Current regulations should be updated to reflect new data sources and methodological guidance will need to be developed.

Develop quality standards for databases, to ensure data are of high quality. Data reporting guidelines should define how data should be collected, coded and cleaned and set out measures to check internal consistency. Gold standards should be established for each dataset.

Theme 3: Leverage current infrastructure and initiatives

Derive value from the existing data infrastructure and systematically evaluate NHS datasets such as Hospital Episode Statistics and explore how they might include more clinical information and be feedback more actively into guidelines and clinical practice. The group considered it important to ensure that people who collect data benefit from feedback and research using the data so they can see the value of what they are doing.

Scale up initiatives that are working well, such as the Salford Lung Study.

Further develop the national infrastructure for data science, with initiatives such as the proposal for a new MRC National Institute for Health and Bioinformatics.

Think globally and consider how the UK can contribute to international research programmes.

Meeting participants concluded that the UK has an ideal infrastructure in the NHS to develop research using routinely collected data and growing experience and expertise in

data science. With growing recognition of the importance of research feeding into improving clinical practice and changes in the HTA and regulatory environment for the development of drugs and other medical interventions, it was agreed that measures are needed now to improve collaborative working and to streamline the design and implementation of research using real world data.