BRITISH PHARMACOLOGICAL SOCIETY

Pharmacology, Clinical Pharmacology and the EU Referendum

The British Pharmacological Society is a charity with a mission to promote and advance the whole spectrum of pharmacology. Founded in 1931, the Society now represents over 3,500 members working across academia, industry, regulatory agencies and the health services, and many of whom are medically qualified. Clinical pharmacology is the only medical specialty in the NHS focusing on the safe, effective and economic use of medicines. The Society supports good prescribing in the UK, most recently notably by developing the Prescribing Safety Assessment with the Medical Schools Council and is interested in:

- Promoting and advancing high quality science, especially pharmacology and clinical pharmacology
- Supporting students and academics in research, as well as the UK university system
- Supporting UK industrial pharmaceutical discovery and development, and underpinning the role pharmacology and clinical pharmacology has to play in that environment

Given that, the Society outlines in the following four sections the areas of the broader pharmacological landscape connected with Europe in a wide range of ways.

1. People: collaboration and mobility

When examining the possible effects of the UK leaving the EU, it is worth considering the value and impact of collaboration in the current 'ecosystem' of scientific discovery.

The UK is undeniably an international leader in scientific research – punching well above its weight. The UK represents only 1% of the world's population, but produces 16% of the world's most highly-cited articles from only 4.1% of the world's researchers. These researchers are highly collaborative, placing the country in a central position to be able to build a network of collaborative partnerships. For example, scientific papers that are co-authored with international researchers have a greater citation impact, than those articles that are not[1]. More than 60% of the UK's internationally co-authored papers are written alongside EU partners[2].

Countries displaying high levels of research collaboration characteristically have high levels of researcher mobility, both of which are associated with high research quality[3]. UK researchers are highly collaborative and mobile across the world[4]. In addition, EU funding mechanisms create opportunities for collaboration. By way of an example, the Marie Skłodowska-Curie Actions enable researchers, from PhD candidates to highly experienced researchers, to work in various countries, sectors and disciplines across Europe[5]. The budget for this programme is €6.16 billion in the period to 2020[6].

Elsewhere, it is possible to see other examples of pan-European collaboration and mobility in support of UK and EU scientific discovery:

- The UK Government provides student loans and maintenance funding for EU students as a statutory obligation[7]
- The university sector contributes over £73 billion annually to the UK economy[8]
- EU nationals make up 15% of the UK-based academic workforce and EU students make up 5% of students in the UK[9]
- At 21%, science disciplines have a higher proportion of EU staff in comparison with 13% across other subjects[10]
- In 2013/2014, EU government bodies funded 8.5% of UK academic staff on fixed-term contracts and other EU sources, 2.1%[11].

And, a little closer to home, examples of relationship with EU can be seen in the British Pharmacological Society's own membership. Of the Society's 800+ members (typically 20% of total membership) based outside of the UK at the start of 2016, around 40% were based in EU countries, and of this group 5% were UK 'ex-pat' pharmacologists living and working in the EU. In addition, of the Society's members based in the UK, 10% are EU nationals.

Question: *How might Brexit affect researcher mobility and high quality science?*

Consideration should be given to:

- Whether or not the UK will benefit from not having to provide students loans and maintenance funding for EU students.
- Whether or not fewer EU students might register at UK universities, if categorised as overseas students at higher fees[12], and what the resultant impact might be on the university sector that contributes over £73 billion annually to the UK economy[13].
- Whether or not there will be an impact on the number of partnerships and highly-cited research projects which are reliant on EU researcher mobility, especially where sustainable funding mechanisms have created opportunities for partnerships.
- The impact of restrictions on mobility on all sectors, including non-academic staff in academia and pharmaceutical industry.
- Whether or not researcher mobility and collaborations that might be built outside of the EU (for example with institutions and individuals in the US) would be enough to sustain and develop the UK research base, should there be a reduction in EU collaborations.

2. Funding

In 2007–2013, the UK contributed €78 billion to the EU of which €5.4 billion was indicated as being for the EU'S Research and Development (R&D) budget. During the same period, the UK received €48 billion, of which €8.8 billion was for research, development and innovation[14]. In other words, the UK received €1 billion per year on average which approximated to 15% of the national science budget during the same period[15]. Overall, the UK won 16% of research funding from the recent European Framework Programme (FP7) with only 12.7% of the EU-28 population[16]. While this funding stream is enormously valuable to the sector, some researchers and members of the Society report significant challenges in access to funding, in particular the complexity of application procedures – so called 'red tape' – which slows funding and grant applications down.

European Research Area and Horizon 2020

The European Commission launched the European Research Area (ERA) in 2000 to coordinate research and innovation activities in the EU. ERA initiatives are delivered through periodic framework programmes[17]. Meanwhile Horizon 2020 is the largest ever EU research programme, aiming to allocate €74.8 billion for research and innovation from 2014 to 2020[18]. The European Research Council allocates funding on behalf of Horizon 2020, and UK universities are expected to receive approximately £2 billion in the first two years of the programme[19].

Question: *In order to sustain science funding at current levels, and to remain competitive with our European counterparts, the UK Government would need to consider matching lost research income (which approximated to 15% of the national science budget during the period of 2007-2013), in the event of leaving the EU[20]. What might the impact be for pharmacology?*

In the event of leaving the EU, there may be two major risks for UK pharmacology in relation to EU funding withdrawal, and the future of the European Medicines Agency (EMA). The 24 Russell Group universities, a number of which teach pharmacology, receive around £400 million of EU funding a year, which makes about 11% of their research income[21]. Losing access to EU research funding may affect not only these but a number of other universities, organisations and bodies receiving EU research funding. It seems uncertain as to whether the UK will be able to stay in the ERA or retain its association with Horizon 2020 and influence the direction or focus of future programmes.

Partnerships: Joint Programming Initiatives (JPIs)

JPIs are public-public research partnerships between ERA countries. Common research agendas are agreed by participating countries to implement jointly. There are currently ten JPIs and the UK participates in all of these joint programmes[22]. Two of these programmes have a pharmacological aspect:

- Alzheimer's and other Neurodegenerative Diseases
- Antimicrobial Resistance- The Microbial Challenge - An Emerging Threat to Human Health

In addition, one of the four programmes initially proposed under Horizon 2020 has a pharmacological angle:

- **European and Developing Countries Clinical Trials Partnership 2 (EDCTP2):** EDCTP is a partnership between 14 African and 14 European countries that aims to support "collaborative research that accelerates the clinical development of new or improved interventions to prevent or treat HIV/AIDS, tuberculosis, malaria and neglected infectious diseases in sub-Saharan Africa"[23]. The UK is one of the 14 European countries. The European Union will allocate up to €683 million for the 10-year programme (2014–2024), to be matched by contributions from the European Participating States.

Partnerships: Joint Technology Initiatives (JTIs)

JTIs are public-private research partnerships between industry and EU member states. The current JTIs are active in a number of areas of strategic importance for the EU[24]. The largest public-private initiative has a pharmacological and pharmaceutical angle:

- **Innovative Medicines Initiative 2 (IMI2):** IMI2 is a joint undertaking between the European Union and the European pharmaceutical industry represented by the European Federation of Pharmaceutical Industries and Associations (EFPIA). The partnership supports collaborative research projects and builds networks of industrial and academic experts in order to boost pharmaceutical innovation in Europe[25]. It has a €3.3 billion budget for the period of 2014–2024[26] (half of the budget comes from Horizon 2020, €1.425 billion committed by EFPIA companies and up to €213 million by other life science industries or organisations).

During the first phase of the programme (2008–2013), IMI1 had a budget of €2 billion, half of which came from the EU's Seventh Framework Programme for research (FP7), and half of which came from EFPIA companies. It currently has over 50 projects focusing on varying topics including broader challenges in drug development like drug and vaccine safety, knowledge management, the sustainability of chemical drug production, the use of stem

cells for drug discovery, drug behaviour in the body, the creation of a European platform to discover novel medicines, and antimicrobial resistance[27]. For example, CHEM 21, a €26.4 million project, brings together six pharmaceutical companies, 13 universities and four small to medium enterprises from across Europe with the aim to develop sustainable biological and chemical alternatives to finite materials. The project is led by The University of Manchester and GlaxoSmithKline and includes Pfizer, the Universities of Durham, York and Leeds and UK-based small to medium enterprises among other European participants[28].

Question: *Would the UK be able to continue taking part in JPIs, e.g. EDCTP2 and JTIs, e.g. IMI2? How would those who were excluded from research cooperation be supported?*

The UK is currently taking part in most joint initiatives. The level of impact from leaving the EU would be different for each project and programme. For example, Norway participates in EDCTP2 and UK may well be able to negotiate its continued participation and contribution along similar lines.

Some projects, however, e.g. CHEM21 led by The University of Manchester and the GlaxoSmithKline, could be significantly affected. Since 2014, Swiss participants are no longer eligible for research funding from the EU and are funded by the Swiss Secretariat for Education, Research and Innovation (SERI). In addition, the Federal Council directly supports those who have been excluded from research cooperation[29].

3. Regulation

The UK is subject to EU legislation that has an impact on a number of pharmacology-relevant areas, e.g. pharmaceuticals, the working hours of doctors, clinical trials directive, directive 2010/63/EU on the protection of animals used for scientific purposes, and others. In return, the UK contributes to wider EU law in a variety of ways. For example, the Academy of Medical Sciences contributed to and led pan-European statements on research regulation and EU Research and Innovation strategy, and recently the Clinical Trials and Data Protection Regulations[30]. The Medicines and Healthcare products Regulatory Agency (MHRA) is a leading contributor to EU law and is respected internationally as one of the leading regulatory authorities for medicines and medical devices[31].

Clinical Trials Regulation

All clinical trials implemented in the EU are required to be conducted in accordance with the Clinical Trials Directive 2001/20/EC until the new Clinical Trials Regulation (CTR) EU No 536/2014 becomes applicable some time after 28 May 2016. The UK had played a

significant role in influencing the improvements to the clinical trials regulation[32]. The EMA was commissioned to establish an EU portal and database as a single entry point for submission of data and information relating to clinical trials required by the Regulation[33]. The House of Lords' Science and Technology Select Committee's report "EU membership and UK Science"[34] notes that clinical trials regulations were "highlighted as causing UK business and research to be disadvantaged compared to competitors outside the EU" by the UK science community. However, the development of the new clinical trials regulation is seen as a considerable improvement.

Directive 2010/63/EU on the Protection of Animals Used for Scientific Purposes

Directive 2010/63/EU governs animal research in the EU. Revising the earlier Directive 86/609/EEC, it was adopted on 22 September 2010 and is based on the principle of the three Rs, to replace, reduce and refine the use of animals used for research[35]. Article 2 of the Directive outlines that member states can maintain stricter provisions aimed at ensuring more extensive protection of animals which were in force on 9 November 2010[36]. Recently, the European Commission had started an infringement process against Italy concerning the overly stringent transposition of the Directive, as stricter provisions were not in force in the country before this date[37]. In the UK, revised legislation transposing the new Directive came into force on 1 January 2013[38]. The House of Lords' Science and Technology Select Committee's report "EU membership and UK Science" highlights the UK's involvement in the development of the framework.

European Medicines Agency (EMA)

Located in London, the EMA is responsible for the scientific evaluation, supervision and safety monitoring of medicines developed by pharmaceutical companies for use in the EU (since 1995)[39]. It is the largest EU body in the United Kingdom with a full-time staff of more than 600 people. British experts were leaders or co-leaders in examining 27 new drug applications in 2014[40].

Question: *In the event of Brexit, how would the Government tackle the regulatory infrastructure changes, particularly in relation to EMA?*

A number of industry officials believe that the EMA would relocate from London to another member state in the event of Brexit[41]. The Swedish pharmaceutical association expressed interest in making Sweden the new host country for the EMA as a major boost for the country's entire life sciences field[42]. In case of relocation, UK could still continue its relationship with EMA and benefit from centralised marketing authorisations as Iceland, Lichtenstein and Norway are included for the latter. Otherwise, pharmaceutical companies will need to apply for marketing authorisations separately to the MHRA for every medicine they would like to supply in the UK[43]. Overall, the status of the MHRA would change and

the organisation would potentially grow. Simultaneously, the MHRA would lose some of its ability to influence regulations due to the withdrawal from the EU platform.

The Unified Patent Court (UPC)

The agreement to create a unified patent court was signed by 25 EU Member States on 19 February 2013[44]. According to the agreement, the UPC will comprise of Court of First Instance, a Court of Appeal and a Registry. The Court of First Instance will be composed of a central division in Paris with two sections in London and Munich and local and regional divisions. The London section will be responsible for "Human necessities" and "Chemistry, metallurgy"[45]. There is a concern that the section of the Unified Patent Court will have to relocate from London before it even opens[46].

The European Strategy Forum on Research Infrastructures (ESFRI)

The ESFRI is a multi-disciplinary forum to support a coherent and strategy-led approach to policy-making on Research Infrastructure (RIs) in Europe and to facilitate initiatives leading to the better use and development of RIs[47]. All EU Member States are represented by two delegates on ESFRI including a number of Associated Nations. The current Chair of ESFRI is Professor John Womersley, the Chief Executive of the UK's Science and Technology Facilities Council[48]. The following landmarks that are pharmacology-relevant (health and food section) were identified in ESFRI Strategy Report on RIs (2016):

- **BBMRI ERIC** - Biobanking and BioMolecular resources Research Infrastructure
- **EATRIS ERIC** - European Advanced Translational Research Infrastructure in Medicine
- **ECRIN ERIC** - European Clinical Research Infrastructure Network
- **ELIXIR** - A distributed infrastructure for life-science information
- **INFRAFRONTIER** - European Research Infrastructure for the generation, phenotyping, archiving and distribution of mouse disease models
- **INSTRUCT** - Integrated Structural Biology Infrastructure

The UK takes part in BBMRI ERIC and INFRAFRONTIER and hosts the headquarters of ELIXIR (Hinxton) and INSTRUCT (Oxford). In addition, the UK hosts the headquarters of the Infrastructure for Systems Biology Europe (ISBE), the ESFRI Project in London (Imperial College London)[49]. As for ESFRI itself, which was setup as an informal forum in 2002[50], Norway and Switzerland participate in the forum and host the headquarters of projects. Given that, the UK is also likely to be able to continue its participation.

4. Impact on the UK pharmaceutical industry

The pharmaceutical industry accounts for 20% of total expenditure on R&D implemented in UK businesses[51]. The sector brings a trade surplus of £3 billion per year[52] but it is safe to say there is some risk to the maintenance of that surplus, should UK vote to leave the EU. For example, the pharmaceutical labour force might be affected by restrictions on mobility, and participation of pharmaceutical companies, particularly small to medium enterprises in EU programmes, e.g. IMI2 would be restricted. In addition, the UK's access to the Small and Medium-sized Enterprises (SME) Instrument – a mechanism that allows EU to support growing businesses – would be under question. The budget for the SME Instrument for 2014–2020 is €3 billion (4% of Horizon 2020)[53].

Some changes would have a bigger impact on the pharmaceutical industry than on the UK pharmacological landscape. Pharmaceutical companies have invested to establish their European headquarters in the UK given the unrestricted access to the EU market. A number of companies based in Japan and USA had selected the UK as their European headquarters. This has contributed to the UK economy and generated job opportunities for UK nationals[54]. Leaving the EU might change the pharmaceutical landscape by prompting companies to relocate their headquarters[55]. HM Treasury has flagged that the benefits of the single market including access to wider market for pharmaceutical companies and their products would be at risk in the event of Brexit[56].

The chief executive of GlaxoSmithKline Sir Andrew Witty noted the benefits of having a Pan-European regulation at the World Economic Forum in Switzerland in January 2016[57]. Pharmaceutical executives believe that the level of fallout from Brexit will depend on whether UK stays part of the EMA. Switzerland, for example, has a separate drug approval process[58].The UK could have a lesser priority in launch sequences of pharmaceutical companies if they were required to seek separate approvals in the UK[59]. In addition, UK pharmaceutical companies could seem less attractive because of tax incentives from business transactions in countries within the EU[60].

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