The Academy of Medical Sciences

Response to BEIS committee inquiry into Brexit and Business: Pharmaceuticals

November 2017

Summary

- Harmonised regulation plays an important role in supporting international collaboration in clinical research and ensuring the monitoring of safety and efficacy of drugs post-licencing.
- The Clinical Trials Regulation will be outside the scope of the EU (Withdrawal) Bill. Clarity is required on how this Regulation will be treated and a high priority should be placed on harmonising to this Regulation and achieving access to the clinical trials registration portal which it will create.
- Continued coordination between the UK's Medicines and Healthcare Products Regulatory Agency (MHRA) the European Medical Agency (EMA) is a mutually beneficial arrangement and should be prioritised.
- The EMA will have to relocate from London to another city within the EU, however this relocation must be managed in a way that preserves the function of the agency at as close to full capacity as possible. The health and safety of patients should not be compromised by a rushed relocation of the agency.
- Science and research conducted within academia and industry is highly international. The UK's future immigration policy must recognise this and provide a fair, transparent and efficient route for strategically valuable individuals to enter the UK. This must not only include research leaders, but also early career researchers, technicians and technologists who support their work.
- The UK's strong life sciences sector is underpinned by its excellent research base. In order to support this strength, the UK should seek the closest possible association with future EU research programmes, which facilitate collaboration and provide an important source of funding for research conducted in universities and small businesses in the UK.
- Access to innovative new medicines may be influenced by the UK's departure from the EU, particularly as the UK represents just 3% of the global market, compared to 25% for the EU. However access must be considered in the context of the wider environment within the NHS, which remains challenging. The implementation of the Accelerated Access Review will help, however continued focus on ensuring rapid access to innovative new treatments for NHS patients is necessary.

Introduction

1. The Academy of Medical Sciences promotes advances in medical science, and works to ensure that these are translated into healthcare benefits for society. Our elected Fellowship includes the UK's foremost medical science experts drawn from the academia and industry. Our submission is informed by the expertise of our Fellowship and elements have been adapted from our submission to a previous inquiry conducted by the Health Select Committee.[1]

2. The UK life sciences sector represents one of the most productive sectors in the UK and is one of the country's great strengths. Life sciences firms require business continuity to support sustained investment in R&D in the UK. This is particularly relevant due to long product development timelines, high risk of failure and lengthy routes to market. The UK's departure from the EU could have profound influence on the pharmaceuticals sector within

[1] The Academy of Medical Sciences (2017). Response to the House of Commons' Health Committee: Brexit – medicines, medical devices and substances of human origin inquiry https://acmedsci.ac.uk/file-download/469033

the UK, both directly through regulation of medical products and clinical research and indirectly through the impact on the underpinning research base.

3. The recently published Life Sciences Industrial Strategy lays out a series of proposals which can support the life sciences sector.[2] However, implementation of this Strategy must be considered in the context of the UK's departure from the EU.

4. EU regulation influences the pharmaceutical sector in many ways. Pan-European regulatory frameworks are important for licencing pharmaceutical products as it can speed up the access to new innovations for patients, either by creating a larger and more attractive market in which to launch a new drug or through facilitating post-licensing surveillance using evidence collected from across the EU.

5. Harmonised regulation can also can facilitate the international collaboration upon which some medical research relies. For example, clinical trials involving rare or childhood diseases, where patient cohorts are small, are often conducted internationally.

6. In order to support the UK pharmaceuticals sector it is imperative to ensure that the UK's exit from the EU does not negatively impact on either the attractiveness of the UK as a market for new drugs or the ability to conduct medical and clinical research in UK businesses and Higher Education Institutes (HEIs).

Regulation

7. There is a need for a regulatory framework which ensures that the UK remains an attractive place in which to conduct research and clinical trials following EU exit, both for academia and for the pharmaceuticals industry. This will be underpinned by the ability to collaborate internationally and therefore the Academy supports continued alignment with EU regulations across many areas of research, particularly around clinical trials.

8. A strong emphasis on harmonisation to existing, or incoming EU regulation can promote continued international collaboration with the EU as well as providing continuity for academia and business. These will include existing regulation of the use of animals in scientific procedures and incoming regulation on clinical trials, medical devices and *in vitro* diagnostics and data protection.

9. With harmonised regulation as the starting point, there may, in time, also be an opportunity to drive the Better Regulation initiative, which seeks to monitor regulatory burdens and to ensure that regulation is better targeted and does not add undue burden to researchers or businesses. Reviewing the regulations of medicines, devices and clinical trials research in this light may reveal possibilities to streamline and improve processes, whilst maintaining strong regulatory standards in the UK. The short term impacts on some specific regulations and relationships with regulators are addressed in turn below.

Clinical Trials Regulation

10. The UK performs strongly in clinical trials compared to other EU countries, consistently hosting the highest number of phase one clinical trials in the EU and ranked in the top two for phase two and phase three clinical trials in 2014.[3]

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[2] https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/650447/LifeSciencesIndustrialStrategy_acc2.pdf

[3] Association of the British Pharmaceutical Industry (2016). Open for Innovation UK Biopharma R&D Sourcebook 2016 http://www.abpi.org.uk/our-work/library/industry/Documents/Open_for_innovation_ABPI_Sourcebook_2016.pdf

11. Furthermore, the UK coordinates the third highest number of pan-European clinical trials and participates in the highest number for rare and childhood diseases. This collaboration is supported by harmonised frameworks for conducting trials.[4] In the future, moves towards precision medicine and more targeted treatments means that trials will increasingly involve smaller patient cohorts and rely on international recruitment.[5]

12. A new EU Clinical Trial Regulation, which will streamline approval processes for international multistate trials and create a new clinical trial registration portal for all trials conducted in the EU was passed in 2014.[6] The new Regulation is widely expected to be a significant improvement on the existing Directive, however it is yet to be implemented. The EMA Management Board recently confirmed that the Clinical Trials Regulation is on course to apply in the second half of 2019 moving this Regulation outside the scope of the EU (withdrawal) Bill.[7,8,9] It remains unclear how these regulations will be treated by the UK, particularly in a potential implementation period.

13. Independent of the delay to the CTR, questions remain about the ability of the UK to access the EU portal from outside the EU. The regulation is not clear on whether non-Member States will be able to access this database. It may be possible for trial sponsors to have access to the portal from outside the EU, however clarity is required from the EMA on this. Maintaining access to the EU clinical trials market and the EU portal is important for pharmaceutical companies wanting to run clinical trials in the UK as well as for academic trials.[10,11]

14. It is possible that there may be some opportunities for the UK by diverging from EU regulation in specific areas, such as single state trials sited in the UK. However, attention must be paid to the opportunity cost of implementing different requirements for UK trials as any benefit could be offset by the difficulties companies might face in navigating different regulations in the EU and the UK, or in affecting the ability of the UK to harmonise for multi-state trials. In addition, concerns have been raised that two parallel systems for single and multi-state trials may add significant burden to UK researchers.

Medicines and European Medicines Agency

15. The licencing of medicines is a currently overseen by the European Medicines Agency (EMA). The presence of the EMA in London has been a major positive for the UK pharmaceuticals industry, providing easy access to the expertise with the Agency. Following EU exit, the EMA will leave the UK and relocate in another EU city, a decision for the future location of the EMA is expected on 20 November 2017.

16. At present the Medicines and Healthcare products Regulatory Agency (MHRA) provides substantial support to the European Medicines Agency (EMA), acting as Scientific Advice Co-ordinator in at least 20% of EMA medicine approvals and conducting a substantial

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[4] Technopolis (2017). The impact of collaboration: The value of UK medical research to EU science and health https://acmedsci.ac.uk/file-download/32381033

[5] EL Jackson, P Feldschreiber, and A Breckenridge (2017). Regulatory Consequences of "Brexit" for the Development of Medicinal Products. Clinical Pharmacology and therapeutics, Vol. 102, no. 2

[6] Regulation (EU) No 536/2014 on Clinical Trials on Medicinal Products for Human Use http://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:32001L0018&from=en

[7] http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2017/10/news_detail_002824.jsp&mid=WC0b01ac058004d5c1

[8] http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000629.jsp

[9] http://www.parliament.uk/documents/commons-committees/science-technology/170921-Robin-Walker-to-Norman-Lamb-DExEU%20letter.pdf

[10] Association of the British Pharmaceutical Industry and BioIndustry Association (2016). Maintaining and growing the UK's world leading Life Sciences sector in the context of leaving the EU http://www.abpi.org.uk/our-work/library/industry/Documents/UK-EU-Steering-Group-Report.pdf

[11] Academy of Medical Sciences (FORUM) (2017). Regulation and governance of health research: five years on https://acmedsci.ac.uk/file-download/14145196

amount of work in inspection and enforcement standards (IE&S) on behalf of the EMA.[12] In addition, the UK has robust data collection which adds significant value to the EMA's EudraVigilance database and the MHRA plays leading role in the European Risk Management Strategy Facilitation Group (ERMS-FG), providing its secretariat and its Pharmacovigilance Business Team. In this way MHRA collaboration with the EMA helps to protect patients across the EU and continued UK access to this database would be mutually beneficial.

17. Furthermore, recent trends to accelerate approval regimes have seen innovative medicines enter the market at earlier stages in their development in the absence of large-scale clinical trial data. These innovative licensing schemes necessitate the need for evaluation of risk-benefit profiles on the basis of much smaller clinical trial data. Therefore, the rigorous collection, monitoring, and evaluation of post-licensing safety and efficacy data becomes increasingly important. This is best conducted at an international level and is currently facilitated by the EMA.[13]

18. For these reasons a continued relationship between the EMA and the MHRA would be mutually beneficial to ensure access to the regulatory expertise within both regulators, protect patient safety and provide business continuity.[14] The UK Government's position is that continued collaboration should be maintained. However, the nature of this relationship is unclear and likely to be influenced by the outcome of negotiations, particularly as the EMA is subject to the European Court of Justice.

19. Due to the lengthy timelines of clinical trials and drug manufacture, urgent clarity is required to reassure businesses, ensure continuity of public health, access to medicines and devices and the development of new treatments.

20. It is the Academy's understanding that the EMA is not legally required to be located in a Member State. Whilst it is understandable that the EMA will need to relocate, this must be done in a manner that preserves the capacity and capability of the agency to fulfil its proper function and thereby does not jeopardise patient safety or access to new and innovative treatments. There is a strong case for the relocation of the EMA to be staggered over an appropriate time period such that its function is compromised as little as possible, preserving public health and providing continuity to deal with more pressing issues such as the implementation of the new clinical trials framework.

Influence

21. It is necessary to recognise that the UK's ability to influence future EU regulation will be diminished following departure from the union. The UK has had significant influence in the development in a number of the EU regulations which influence the life sciences. For example UK leadership on aspects of the General Data Protection Regulation (GDPR) led to a more supportive framework for sharing of personal data in research and the CTR was developed with strong involvement from the UK sector.

22. It is also important to consider the UK's global influence. For example the MHRA will remain a member of the international regulators forum the International Coalition of Medicines Regulatory Authorities (ICMRA), an organisation which brings together medicines regulators from around the globe to drive global co-ordination in the regulation

[12] Technopolis (2017). The impact of collaboration: The value of UK medical research to EU science and health https://acmedsci.ac.uk/file-download/32381033
[13] EL Jackson, P Feldschreiber, and A Breckenridge (2017). Regulatory Consequences of "Brexit" for the Development of Medicinal Products. Clinical Pharmacology and therapeutics, Vol. 102, no. 2
[14] *ibid*

of pharmaceuticals and medical devices the UK can and should continue to engage in this forum.

No deal

23. Should the UK leave the EU without a deal, the MHRA would have to function as a sovereign regulator. The MHRA has retained the capacity and physical capability to do this, particularly if it was no longer required to conduct work on behalf of the EMA. However, the MHRA would face funding challenges if it were required to do so. For medicines assessment the MHRA is fully funded by fee income and a significant portion of this money comes from work done on behalf of the EU. This income would be lost if cooperation between the MHRA and EMA were to cease. Moreover, should the MHRA become a sovereign regulator, industry would face the prospect of paying both a UK licensing fee and an EU fee.

24. Currently, as part of the EU regulatory framework, all medicines are tested and released by a Qualified Person in one member state for use across the whole EU. After EU exit, if the UK is no longer part of this regulatory framework, this testing process would need to be replicated in both the EU and UK. A mutual recognition agreement would prevent the need for duplicative testing and facilities, thereby providing some continuity for the sector.

Skills

25. Attendees at a recent event on the UK Drug Discovery Landscape hosted by the Academy's FORUM and the Association of the British Pharmaceutical Industry (ABPI) noted that recent trends within the pharmaceuticals industry away from in-house R&D are generating skills shortages in some areas. As well as training staff to fill these gaps, delegates emphasised that ensuring access to international talent is central to maintaining a high quality and diverse skill set in drug discovery in the UK. There was agreement that it will be important to ensure that the UK can continue to recruit, and engage with, the best talent from abroad following EU exit.[15]

26. The Academy of Medical Sciences does not have access to information on the nationalities of those working within the pharmaceuticals sector, however we wish to highlight the international nature of research and development, particularly within HEIs where a substantial proportion of staff in research and/or teaching positions come from non-UK EU countries. HESA data from 2015/16 indicates that for medicine, dentistry and health, individuals from EU countries outside the UK make up 38% of research staff and 12% of those who do both research and teaching. For the biological, mathematical and physical sciences, individuals from EU countries outside the UK make up 32% of research staff and 19% of those who do both research and teaching.

27. Alongside those on research and/or teaching contracts it is also important to consider the importance of technicians and technologist who support research activities within HEIs and businesses. Analysis of technicians employed by Russell Group Universities (RGUs) revealed that there are approximately 9000 technicians at RGUs with over half of these employed in the areas of the life sciences, broadly defined. Of the total 9000 technicians, approximately 9% are from EEA countries.[16]

28. Under present rules, recruitment of non-EEA personnel to these roles is challenging as often neither the salary nor job requirements makes them eligible under the Tier 2 visa.

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[15]Academy of Medical Sciences (FORUM) (2017). The UK drug discovery landscape https://acmedsci.ac.uk/file-download/71272985

[16] Russell Group (2017). Impact of Brexit on the technical workforce at Russell Group universities. http://www.russellgroup.ac.uk/media/5571/impact-of-brexit-on-the-technical-workforce-september-2017-final.pdf

This is in contrast to the fact that 90% of technicians are qualified to NQF6 and above and 25% have a PhD.[17] According to the Russell Group if existing immigration for Tier 2 visas were applied to EU nationals post-Brexit, universities would struggle to recruit appropriately skilled staff for technical positions, which in turn would impact on the research within UK universities.[18]

29. The Academy has consistently called for clarity on the settlement status of EU nationals resident in the UK. Following exit from the EU, the strength of the UK life sciences sector will depend upon a transparent, fair and efficient immigration system which welcomes the best research talent as well as those who provide the technical skills which support this research.[19] A pragmatic approach to the immigration status of dependants will be essential to attracting and retaining the talent that the life sciences sector and academia require.

Research and Development

30. EU funding sources support research and development activities which takes place in a range of settings, including HEIs and for-profit companies, in particular small and medium enterprises (SMEs). UK HEIs and SMEs have benefitted from a wide range of EU funding sources, for example, between 2007 and 2013 (Framework Programme 7) UK businesses received over £1 bn worth of R&D funding. This represented a relatively small proportion of total Business Enterprise investment in R&D in this period (detailed in Table One), however it comprised almost 17% of all R&D investment by SMEs. In fact, UK SMEs were more successful at drawing down EU funding than any other member state, securing £658 million from Framework Programme 7.[20] Whilst these data are not specific to the pharmaceuticals sector they do demonstrate the importance of EU funding to UK SMEs conducting R&D.

Table One: EU Framework Programme funding granted to UK for-profit companies under Horizon 2020[21]

	FP7 funding (2007-2013) [1]	Business Enterprise R&D (2007-2013)	FP7 funding as proportion of Business Enterprise R&D expenditure (2007-2013)
UK SMEs	£ 658m	£ 3,885m	16.9%
UK large businesses	£ 354m	£ 112,660m	0.3%
All UK businesses	£ 1,012m	£ 116,545m	0.9%

31. Analysis of the UK participation in the Innovative Medicine Initiative (IMI) reveals more sector-specific insight. IMI is the largest public private partnership in the life sciences and was established by the Joint Technology Initiative with the aim of improving the drug

[17] *ibid*
[18] *ibid*
[19] Academy of Medical Sciences, the British Academy, the Royal Academy of Engineering and the Royal Society (2017). Joint submission to the House of Commons Home Affairs Committee inquiry on immigration https://acmedsci.ac.uk/file-download/12658478
[20] Technopolis (2017). The role of EU funding in UK research and innovation https://acmedsci.ac.uk/file-download/70343877
[21] adapted from Technopolis (2017). The role of EU funding in UK research and innovation https://acmedsci.ac.uk/file-download/70343877

development pathway through collaborative efforts between organisation and institutions across the pharmaceutical sector. Half of the funding is contributed by the European Commission (EC), which must be matched in kind by members of the European Federation of Pharmaceutical Industries and Associations (EFPIA) and other associated partners.[22] EFPIA members are not eligible for funding from the EC, however SMEs may obtain funding. UK SMEs have won 21% of total IMI funding awarded to SMEs (between 2008 and 2016), the highest of any nation.[23]

32. Attendees at a recent event on the UK Drug Discovery Landscape noted above highlighted the importance of maintaining access to the IMI and other initiatives which incentivise and support international collaboration following UK exit from the EU.[24]

33. In the long-term the Academy believes that UK research would be best served by the closest possible association with EU research programmes in any future relationship. We welcomed the Government's recent discussion paper outlining the UK Government's desire for an "ambitious" future relationship with EU research and innovation, however further clarity on the nature of this relationship is urgently required.[25] The EU Commission's High Level Group on maximising the impact of EU Research & Innovation Programmes LAB-FAB-APP report called for full and continued UK participation in future framework programmes, noting that this would be mutually beneficial to the UK and EU27.[26]

Transitional arrangements

34. The Academy welcomes calls for an implementation period that reflects the time needed to make any necessary adjustments to ensure continuity for research and business, which will be of benefit to both the UK and the EU. Transitional arrangements which are in the interests both of the public and of industry must be agreed. As noted above, a high priority should be given to ensuring the continuity of function of the EMA during a transition period. This is particularly pertinent during the relocation of the agency, which should be conducted in a phased way in order to ensure its capacity is maintained at the highest levels possible during the transfer to its future location.

35. It remains unclear how the CTR will be treated during a potential implementation period. An additional two years to establish the future relationship would be beneficial if it acts as a stepping stone to long-term harmonisation and access to the EU portal. However if harmonisation and access to the portal would only be achieved in the short-term, this would not provide the desired continuity.

Access to medicines

38. Pharmaceutical products often rely on supply chains which span borders. According to the Brexit Health Alliance (BHA) *"It is not uncommon for a 'British' product to have touched 7 other jurisdictions before reaching the market place."* Any changes to trading agreements following EU exit may affect the ability of suppliers to move these products and supply chains could be disrupted. The BHA suggest that *"these factors could also make the UK an*

[22] Technopolis (2017). The role of EU funding in UK research and innovation https://acmedsci.ac.uk/file-download/70343877
[23] Association of the British Pharmaceutical Industry (2016). UK Participation in the Innovative Medicines Initiative http://www.abpi.org.uk/our-work/library/industry/Documents/UK_Participation_in_IMI.pdf
[24] Academy of Medical Sciences (FORUM) (2017). The UK drug discovery landscape https://acmedsci.ac.uk/file-download/71272985
[25] https://acmedsci.ac.uk/more/news/dexeu-publishes-position-paper-on-science
[26] https://ec.europa.eu/research/evaluations/pdf/archive/other_reports_studies_and_documents/hlg_2017_report.pdf

unattractive market for producers and when supplies were low, the UK would not be a priority."[27]

39. Access to new medicines may also be affected by UK exit from the EU. The UK represents 3% of the pharmaceuticals global market, whilst the EU represents 25%. If the MHRA is to become a sovereign regulator it must overcome this reality in order for the UK to remain an attractive market place for medicines. Options may exist to address this concern by developing rapid targeted approval processes and managed access agreements to ensure continued timely access to new medicines in the UK.

40. Access to new medicines following UK departure from the EU must also be placed in the context of the wider issues of access to medicines within the NHS. Access to innovative treatments in the NHS is often slow and the route to market for innovative products developed by the UK's life science's sector is not straightforward. The Academy welcomed the recent Government response to the Accelerated Access Review (AAR) and the investment of £86 million to support its implementation.

41. Addressing the challenge of access to new innovation within the NHS must include recognising a broader definition of "value" of products to reflect their true worth. New models for pricing and reimbursement can offer a more pragmatic, affordable solution for the healthcare system by more closely aligning price with value. This more holistic and longer-term approach can drive uptake and adoption in the NHS. Furthermore the incorporation of new forms of evidence and holistic definitions of value within the decision making process will help the National Institute of Health and Clinical Excellence to maintain and build on its significant global influence.

42. Nevertheless, the recent Budget Impact Threshold (BIT) by NICE did not provide reassurance that access to and uptake of innovation in the NHS will improve in the short term. The introduction of BIT would likely result in delays in accessing new and innovative treatments for patients and is not compatible with making the NHS an attractive market for new drugs.

This response was prepared by Dr Tom Livermore (Senior Policy Officer) and was informed through the Academy's previous activities. For further information, please contact tom.livermore@acmedsci.ac.uk; +44(0)20 3141 3220.

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[27] Brexit Health Alliance (2017). Collective "asks" as the UK negotiates to exit the EU http://www.nhsconfed.org/~/media/Confederation/Files/public%20access/European%20Office/Brexit%20Health%20Alliance%20Asks.pdf