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Summary

- The development of, and access to, medicines and medical innovations are subject to EU regulations and EU licencing.
- Harmonised regulation plays an important role in the supporting international collaboration in clinical research and ensuring the monitoring of the 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 in 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. Public health should not be compromised by a rushed relocation of the agency.
- UK notified bodies oversee the assessment and CE marking of more than half of the highest-risk medical devices on the EU market. Any change to the recognition of decisions of UK notified bodies would have a major impact on the approval of these devices across the EU.
- 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 campaigns to ensure that these are translated into healthcare benefits for society. Our elected Fellowship includes the UK's foremost experts drawn from the medical sciences. Our submission is informed by the expertise of our Fellowship and has been contributed to by the Royal Academy of Engineering.
2. The UK's departure from the EU could have profound influence on the regulation of medical research and the development of, and access to, innovative new treatments. EU regulation influences research and innovation both directly, such as in the use of animals in research, and indirectly, through the incoming regulation on personal data. Harmonised regulatory frameworks 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. Harmonised processes for licencing the products of medical innovation 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 safety and efficacy testing using evidence from across the EU.
3. Therefore, ensuring that the UK's exit from the EU does not negatively impact on either the ability to conduct medical and clinical research in the UK, nor on the ability of patients in the UK, and the EU, to access the outputs of this research must be a key priority for both the UK Government and the European Commission.

Key considerations for companies and regulatory authorities

4. There is a strong 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. 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.
5. 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. 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

6. The UK coordinates the third highest number of pan-European clinical trials and the highest number for rare and childhood diseases. This collaboration is supported by harmonised frameworks for conducting trials.¹ Furthermore, moves towards precision medicine and more targeted treatments means that many trials will increasingly involve smaller patient cohorts and rely on international recruitment.²
7. 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. The new Regulation is widely expected to be a significant improvement on the existing Directive, however it has 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.^{3,4,5} It remains unclear how these regulations will be treated by the UK, particularly in a potential implementation period.
8. Independent of the delay to the CTR, questions remain about the ability of the UK to access to 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.
9. 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.⁶ Aligning to the CTR and gaining access to the EU portal should therefore be seen as a high priority.
10. Once this has been achieved there may be opportunities, through the Better Regulation initiative to explore possibilities for a national approach that could play to existing UK strengths in early

¹ Technopolis (2017). The impact of collaboration: The value of UK medical research to EU science and health

² 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

³ http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2017/10/news_detail_002824.jsp&mid=WCOB01ac058004d5c1

⁴ http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000629.jsp

⁵ <http://www.parliament.uk/documents/commons-committees/science-technology/170921-Robin-Walker-to-Norman-Lamb-DExEU%20letter.pdf>

⁶ 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>

stage clinical trials and allow increased agility to build on these. However, this must be weighed up against the potential burden associated with operating under two systems and the increasing move to precision trials where smaller patient numbers make cross-border trials more commonplace.

Devices and Diagnostics

11. New EU legislation to regulate medical devices and In vitro diagnostics (IVD) has been passed, but will not come into force until 2020 and 2022 respectively. This legislation represents an improvement on existing regulation, providing a more robust regulatory framework for devices, including more emphasis on evidence generation around their effectiveness.⁷ In September, Lord O'Shaughnessy assured that the EU (withdrawal) Bill in its current form would transpose these regulations into UK law.⁸
12. There is strong support in the sector for maintenance of regulatory alignment for devices between the UK and EU. A survey by the Association of British Healthcare Industries found that only 3% of members who responded supported regulatory divergence with the EU. Continuity in the CE marking system will ensure that products developed in the UK continue to be recognised in the EU and around the globe, and that products developed in the EU can continue to be recognised in the UK. This is important to maintain NHS patient access to innovative devices, and facilitate access for UK device companies to the EU and broader market. The system of Notified Bodies granting CE marks should therefore be maintained. This system is already operating in non-EU jurisdictions including Turkey and Switzerland.
13. The UK has five Notified Bodies and clarity is required on whether their decisions will continue to be recognised by the EU, as this will not follow automatically from the adoption of the new EU regulations. UK Notified Bodies oversee between 50 and 60% of all the highest-risk devices on the EU market.⁹ Therefore, any change to the recognition of the work of UK and EU Notified Bodies is likely to have an impact on the capacity of the system. Therefore mutual recognition in this area should be explored.
14. As with the CTR, incoming regulations will introduce new central EU databases, which will collate information for traceability, post-market surveillance and clinical evaluation data. UK access to these databases could be valuable for transparency and traceability of devices.
15. In addition, many devices and diagnostics use the relevant European harmonised standards, produced by the European Standardisation Organisations, to demonstrate compliance with regulation. Given its current level of engagement and expertise, the UK's continued membership of European Standards Organisations would be desirable and would preserve UK influence in the development of European standards relevant to medical devices. The British Standards Institution, as the UK representative, is working with these organisations on potential mechanisms for maintaining UK membership following Brexit.

Medicines and European Medicines Agency

16. The licencing of medicines is 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

⁷ Academy of Medical Sciences and Royal Academy of Engineering joint response to MHRA consultation on the revision of European legislation on medical devices. 2013

⁸ <https://www.gov.uk/government/speeches/lord-oshaghnessy-on-medical-technologies-and-brexite>

⁹ 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>

UK and relocate in another EU city, a decision for the future location of the EMA is expected on 20 November 2017.

17. EMA staff were recently surveyed regarding their intentions to remain with the Agency as it leaves the UK. For some locations, more than 70% of staff indicated that they would not be prepared to relocate. The EMA estimated that staff loss of this scale could lead to an inability of the EMA to operate and may precipitate a “public health crisis” from which the regulator could not recover.¹⁰ The EMA also estimates that even for relocation those candidate cities which would result in the least staff losses (~20%), the agency could take 2-3 years to recover full to capacity.
18. 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.
19. 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 amount of work in inspection and enforcement standards (IE&S) on behalf of the MHRA.¹¹ As well as licensing of new drugs, the EMA also conducts post-marketing efficacy and pharmacovigilance studies across the EU. For example, the agency coordinates pharmacovigilance data from 28 member states through its EudraVigilance database.¹² The UK has robust data collection which adds significant value to the data captured in this database and the EMA 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 eth EMA helps to protect patients across the EU and continued UK access to this database would be mutually beneficial.
20. 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 further 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
21. 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 and protect patient safety.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.
22. Due to the lengthy timelines of clinical trials and drug manufacture, urgent clarity is required to ensure continuity of public health, access to medicines and the development of new treatments.

¹⁰ http://www.ema.europa.eu/docs/en_GB/document_library/Other/2017/09/WC500235516.pdf

¹¹ Technopolis (2017). The impact of collaboration: The value of UK medical research to EU science and health

¹² http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000679.jsp

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*

23. It is also important to highlight that the UK's membership (through MHRA) of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) is dependent on EU membership. It can take up to 2 years to gain membership to ICH and the UK should act now to ensure continuity in representation in this international forum.

Life Science Industrial Strategy

24. 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-developmental timelines, high risk of failure and lengthy routes to market. The recently published Life Sciences Industrial Strategy lays out a series of proposals which can support the life sciences sector. However, implementation of this Strategy must be considered in the context of the UK's departure from the EU, which will influence many aspects of the strategy, including through regulation of research, medicines and medical devices as outlined above

Alternative arrangements

25. 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 to do this, however it 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.

Transition period

26. The Academy welcomes calls for an implementation period that reflects the time needed to make any necessary adjustments to ensure continuity for research, 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. A high priority should be given to ensuring the continuity of function of the EMA during a transition period.
27. 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.
28. The immigration status of EU nationals, including researchers, regulators and clinical staff in the UK remains the key issue for the sector. Long-term clarity is urgently required. An implementation period must not add a further two years of uncertainty to the status of non-UK EU researchers in the UK.

Influence

29. It is necessary to recognise that the UK's ability to influence future EU regulation will be diminished. 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.

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

Medical radio-isotopes

31. Following the decision to leave the EU, the UK government has committed to withdrawal from the Euratom community, which provides access to a single market for trade in nuclear goods and services.¹⁵ Concerns have been raised that leaving Euratom will risk disrupting the supply chain of radioisotopes important for nuclear medicine and research.¹⁶ The Government's position remains that supply of radioisotopes will not be affected and a new Nuclear Safeguards Bill has been announced to establish a safeguards regimen following departure from the Euratom community.¹⁷
32. By March 2019 the UK must ensure that a new regulatory body is established to replace Euratom and ensure effective safety legislation covering exposure to radiation. The newly introduced Nuclear Safeguarding Bill is intended to do the former, whilst BEIS are consulting on the later.^{18,19} There is still concern in the community about whether medical procedures and research will be affected indirectly on the leave date, particularly for isotopes with very short half-lives, which would be disproportionately affected should there be delays in the import of radioisotopes.²⁰
33. The most pressing concern for medically-relevant isotopes is molybdenum-99 and its decay product technetium-99m (^{99m}Tc), which are used for medical imaging purposes. Molybdenum-99 has a half-life of 66 hours and disruption to its supply is of serious concern to the UK. The UK does not produce molybdenum-99, making it vulnerable to any problems with shipping and importation as well as global shortages.²¹ In response to global shortages in 2009-10, the European Observatory on the supply of medical radioisotopes was created.²² The observatory has a mission to ensure security of supply of medical radioisotopes for all members of Euratom, the UK's future relationship with this observatory following EU exit remains unclear.

Access to new medicines/innovation

34. 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.
35. 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 investment of £86 million to support the Accelerated Access Review (AAR) and improve the capacity of the NHS as a

¹⁵ http://www.legislation.gov.uk/ukpga/2017/9/pdfs/ukpgaen_20170009_en.pdf

¹⁶ <https://www.bnms.org.uk/news/press-release-british-nuclear-medicine-society-statement-on-leaving-auratom.html>

¹⁷ <https://www.gov.uk/government/publications/nuclear-safeguards-bill-summary-factsheet>

¹⁸ <https://publications.parliament.uk/pa/bills/cbill/2017-2019/0109/18109.pdf>

¹⁹ Revised requirements for radiological protection: regulation of public exposures and the justification of practices <https://www.gov.uk/government/consultations/revised-requirements-for-radiological-protection-regulation-of-public-exposures-and-the-justification-of-practices>

²⁰ <https://www.bnms.org.uk/news/press-release-british-nuclear-medicine-society-statement-on-leaving-auratom.html>

²¹ http://www.iop.org/policy/consultations/file_69693.pdf

²² http://www.iop.org/policy/consultations/file_69693.pdf

place in which to test innovative products. We look forward to the Government's full response to the AAR, which must build on this announcement.

36. 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.
37. 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 and through consultation. For further information, please contact tom.livermore@acmedsci.ac.uk; +44(0)20 3141 3220.

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