House of Commons Health Select Committee – Brexit and medicines inquiry

AoMRC submission with contributions from FPM/RCP/RCR

Introduction and Background

The Academy of medical Royal Colleges is the coordinating body for the UK and Ireland's 24 medical Royal Colleges and Faculties. They ensure patients are safely and properly cared for by setting standards for the way doctors are educated, trained and monitored throughout their careers.

This submission has been led by Professor Alan Boyd, President of the Faculty of Pharmaceutical Medicine, on behalf of the Academy of Medical Royal Colleges' Council, and with contributions from Professor Margaret Johnson, Academic Vice-President, Royal College of Physicians, London and Professor Nicola Strickland, President of the Royal College of Radiologists.

Responses to Inquiry Questions

1. **What are the key considerations that arise for companies, healthcare services and regulatory bodies in the UK as a result of the UK's withdrawal from the EU? Focussing on patients and the public, what needs to be done to ensure that any adverse impact is minimised or eliminated, and that opportunities to enhance services are maximised?**

The UK has been a pioneer in the establishment of systems for the approval and reimbursement of medicines, and has a concentration of expertise and resource – including the NHS, National Institute for Health and Care Excellence (NICE), internationally renowned academic centres and multinational pharmaceutical companies. We have played a leading role within the European Medicines Agency (EMA) since its creation and currently handle about one third of all new applications on behalf of the EMA (within the Medicines and Healthcare products Regulatory Agency (MHRA)).

In relation to pharmaceutical companies, the UK market for prescription medicines and devices comprises only about 10% of the total market for prescription medicines in Europe. Therefore, following the UK's withdrawal from the EU, there is a very real risk that pharmaceutical companies may have less incentive to prioritise the UK as a key market. They may prefer to conduct clinical trials within the EU and will submit their marketing authorisation applications (MAAs) to the (EMA) in the EU as well as to the FDA in the USA. Because of this, UK doctors serving as clinical trial investigators will not have the front-line experience of using new medicines in development and access to these medicines will be delayed, quite possibly by some years. Ultimately, patients will see a significant delay in being able to access new therapies and new medical technologies, and will undoubtedly suffer consequently.

In relation to healthcare services, the UK is a net beneficiary for research grants and one of the most successful countries at securing funding. The EU research and innovation budget for 2014-2020 is around €120bn[1]. Innovation and progress are not possible without funding. The ability to secure research grants and be a part of EU wide clinical trial research projects will have a direct impact on our ability to secure good patient outcomes, particularly for rare conditions. Projects funded by the

[1] 'Overview of EU funds for research and innovation', EU Parliament, September 2015

EU have enrolled over 340,000 patients[2] to clinical trials so far[3] with the UK leading the way in Europe for conducting clinical trials.[4]

The Government must urgently clarify the status of current regulations particularly regarding access to medicines, clinical trials and employment related areas such professional qualification recognition and equability from the date of the UKs withdrawal from the European Union to reduce uncertainty and confusion with sufficient time allowed for any changes to be implemented.

Recommendations:

- *That the UK maintains a system for rapid review and approval of novel clinical trials so that it remains a key country for the conduct clinical research;*
- *Maintain on-going work to develop clinicians as key investigators with the appropriate training and supports;*
- *Keep costs for approving and delivering clinical trials in the UK competitive so companies are incentivised to come to the UK.*
- *Within the UK focus on innovative adaptive licensing processes with a closer alignment of the regulator and health technology assessments.*
- *Consider developing a system of rapid access for medicines with a serious unmet medical need as recommended in the Life Science Industrial Strategy Review and the Accelerated Access Review.*
- *Work with the EC/EMA to ensure that the UK maintains its membership of European (non-EU) public health networks, for instance in pharmacoepidemiology, to which the UK has been a significant contributor.*

Response Word Count: 580

2. Following the UK's withdrawal from the EU, what alternative arrangements for the regulation of medicines, medical devices, medical products and substances of human origin could be introduced? What are the respective opportunities, risks and trade-offs involved?

The UK should ideally seek to continue to operate as a full member of the EMA, as it has done since the federal agency was established. However, in the situation that the UK is not able to continue its current membership of the EMA, and the UK adopts a separate regulatory pathway, then this must be seen as being a primary pathway for review, aligned to the timings for EMA and FDA review, or even as a more rapid pathway to obtain marketing authorisation. The MHRA could 'recognise' approvals by the EMA and only oppose a registration if there are strong safety or efficacy reasons that are identified that could impact on patients. In addition, a separate regulatory pathway in the UK could be aligned with reimbursement given that this is seen as a significant rate-limiting step to patient access, particularly for orphan diseases.

Regardless of direction of the future arrangements with the EU, the UK must continue to play a full part in major international organisations (e.g. WHO) and agreements, particularly ICH (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use), as this has been accepted by the three major markets, (EU, USA and Japan) and any departure from this will be detrimental to the UK's credibility. This will mean that there will be considerable concurrence between MHRA and EMA as both will follow the same agreements. In any

[2] 'What implications could Brexit have for NHS patients?', NHS Confederation, July 2016
[3] 'What implications could Brexit have for NHS patients?', NHS Confederation, July 2016
[4] 'Patient access to medical innovation under threat from Brexit' ABPI, May 2016

event the UK must continue to be an important contributor to any changes in these regulations with a seat at the table.

If MHRA accept the same regulatory dossier that is also submitted directly to the EMA then this will reduce some anxiety of sponsors that the UK is a completely separate process and so may not be a first line submission. It would then potentially be advantageous for both MHRA and EMA reviews to follow similar times and perhaps to have joint oral presentations, if needed.

Recommendations:

- *The MHRA should retain its membership of the EMA, and continue with an active role in EU regulations development and product review.*
- *Ensure that the MHRA is adequately resourced to perform rapid review of marketing authorisation applications for novel therapies, whilst also maintaining current regulatory standards and at a fee level which is competitive with other major regulatory authorities.*
- *Consideration should be given to conducting the regulatory review and reimbursement procedure in parallel, allowing for more rapid access to medicines post-marketing authorisation. Reimbursement could allow for 'conditional' approval, with review following a defined period in the market and additional clinical data collection, for those medicines with limited data and where a serious unmet medical need has been identified.*

Response Word Count: 441

3. How much time is needed to facilitate a smooth transition to new arrangements? Is it possible, or desirable, to move directly to new arrangements post-29 March 2019, or are transitional arrangements needed?

If an agreement can be reached by the end of March 2019 that is acceptable to both parties, then there may be no need for any transitional arrangements. However, it should be noted that when significant changes have occurred in the past in relation to the medicines regulations across the EU, then there has always been a transitional period put in place to allow for the changes to occur. Given the complexities around medicines regulations and the fact that many of them relate to the safety and protection of patients, it would seem appropriate that any changes that are introduced are made in a controlled fashion so that no patient is put at risk by making any change suddenly.

In addition, there are some key roles that individuals undertake which are closely linked to the execution of the procedures that are part of the regulations. Examples are the Qualified Persons for Pharmacovigilance (QPPV) and the Qualified Persons for Manufacturing (QP). For these individuals that carry out these specific roles there is a requirement within the regulations that they reside within a country which is part of the EU. Recently the EMA have notified all QPPVs and QPs who currently reside in the UK that at the end of March 2019 that they will need to relocate to another EU Country if they want to continue working in these defined roles. Given that approximately one-third of all the EU QPPVs reside within the UK it is unrealistic to expect them to relocate in such a short space of time and therefore this should be managed via a transition period of some kind. The same principle will apply to the QPs.

Also, depending upon the relationship that is agreed between the UK and the EMA, there is a possibility that it will be necessary for the MHRA to establish its own medicines regulations and put procedures in place to continue to ensure that patient safety is paramount. Again, this will take time to establish new procedures and operations and a transition period to allow this to happen would be advisable.

Other points to consider is that, given the majority of medicines are regulated at the federal level of the EU rather than via national agencies, putting transitional arrangements in place to ensure a smooth handover of responsibilities will be important. It all needs to be emphasised that all medical devices and in vitro diagnostic devices are regulated at the federal level of the EU via the CE marking process and not at all national level at all. Given that there are many thousands of medical devices available, it will only be appropriate to cover any changes to the authorisation and use of such products over a period of time.

Recommendation:

- *Given the complexities of setting up new procedures for the regulation of medicines and medical devices, it is in the interest of patient safety that a transition period of at least two years post-29 March 2017 would be advisable.*

Response Word Count: 497

4. How will withdrawal from the European Union affect the UK's ability to influence international standards in life sciences?

The UK's withdrawal from the EU places the UK's ability to influence international life science standards at risk. Across a range of areas including the development of EU wide public health initiatives, access to European Reference Networks (ERNs), the ability to share data and access to significant EU research grants all need full and proper consideration.

The UK currently has access and is able to set the direction for research funding from the EU research and innovation budget for 2014-2020 is around €120bn[5]. The UK is a net beneficiary for research grants and one of the most successful countries at securing the funding. The UK should negotiate continued access to funding or provide equivalent replacement funding long-term for research so that patients have access to the best care in the future. The Chancellors announcement of additional research and innovation funding is welcome but it's vital that this funding is secured long term. It should also be noted that even if funding is secured long-term the UK will still see its ability to influence standards reduced, as we will no longer play a role in setting the priorities of the EU research and innovation budget.

European Reference Networks are virtual advisory networks with the coordinators based in 24 hospitals across Europe that aim to tackle complex or rare diseases that require highly specialised knowledge and treatment. It provides patients with rare diseases access to expertise from other countries and provides support to doctors so that they can provide the best treatment possible. The UK currently plays an active role in the ERNs, leading on a quarter of the networks. The UK's withdrawal from the EU places the UK's access to these ERNs at risk which has both an impact on the UK's ability to be a part of these learning networks as well as potentially having an impact on patient outcomes in the UK.

Data sharing between Europe and the UK is essential for public health, medical research and ensuring patient safety. The General Data Protection Regulation (GDPR), which comes into effect May 2018, will provide important protections for individuals, while also allowing data to be shared within the EU. It is currently unclear whether the data will continue to be shared when the UK leaves the EU. Data sharing is important for the delivery of excellent patient care. Sharing data for Europe-

[5] 'Overview of EU funds for research and innovation', EU Parliament, September 2015

wide clinical trials is one example of where data sharing enhances the ability for patients to access new treatments. The UK must retain the GDPR and harmonise legislation on data sharing with the EU to enable it to either be considered equivalent to EU regulation, or have an adequacy arrangement[6]. Without a clear data sharing framework, the UK's influence would be greatly reduced and patient safety is put at risk.

Response Word Count: 565

5. **What arrangements are needed to ensure the safe, effective and timely supply of medical radioisotopes over the short, medium and long-term?**

Radioisotopes play a crucial role in medicine. The majority of the UK's supply of radioisotopes, used in scanning and the systemic and internal treatment of a wide range of cancers, is imported from Europe and further afield. The UK does not produce any radioisotopes made in a nuclear reactor. The clinically most important of these is molybdenum-99 (^{99m}Mo) from which technetium-99m (^{99m}Tc), the most commonly used radioisotope, is derived. ^{99m}Tc is used in 700,000 medical procedures each year.[7] Global demand for ^{99m}Mo is growing by 0.5% a year[8]

The European Atomic Energy Community (Euratom) supports the secure and safe supply and use of medical radioisotopes [9] The UK will be required to withdraw from Euratom when we leave the European Union (EU). Therefore, the UK will no longer have access to Euratom's support, so ensuring a seamless continuing supply must form a key part of Brexit negotiations. The UK should remain part of Euratom during any transition period.

The supply of radioisotopes may also be disrupted if and when the UK leaves the single market as any transport delays will reduce the amount of useful radioisotope because they decay within hours or days of production, ^{99m}Mo has a half-life of just 66 hours. The consequences of a disrupted radioisotope supply have been demonstrated when the Channel Tunnel fire in 2008, led to a reduction of the availability of radioisotopes and to cancelled procedures.[10]

In the short and medium term, similar legislation to that currently governing transport of medical radioisotopes across borders in the EU, must be put in place. This requires detailed discussion by the Government, with key stakeholders, to plan and implement a national strategy on the use of radioisotopes across the UK, which must look at supply, cost and future proofing. When new customs agreements are set up, the arrangements for the importing of radioisotopes must be the same as they are now to ensure there are no delays at the border.

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[6] * Adequacy arrangement: Data adequacy is a status granted by the European Commission to non-EEA countries who provide a level of personal data protection that is 'essentially equivalent' to that provided in European law. It can also be awarded to specified sectors of an economy or international organisations. Currently 12 countries have this status. Source: Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data.

[7] Future Supply of Medical Radioisotopes for the UK, British Nuclear Medicine Society and the Science and Technology Facilities Council, 2014

[8] 2017 Medical Isotope Supply review 99Mo/99mTc Market Demand and Production Capacity Production 2017-2022 OECD Nuclear Energy Agency's High level Group on the Security and Supply of medical radioisotopes 2017 https://www.oecd-nea.org/cen/docs/2017/sen-hlgmr2017-2.pdf

[9] Mission Statement Euratom supply agency

[10] http://www.world-nuclear-news.org/np_isotope_supply_further_tightened_by_transport_restrictions_0110081.html

In the long term, there will need to be sustained and significant investment in the ability of the UK to produce its own radioisotopes. Building a new research nuclear reactor would cost £200-400m and would take ten years[11], so would require investment from the Government or industry.

Recommendation:

- *The UK should consider diversifying its strategy of reliance on reactor-based* ^{99m}Mo *and support the development of non-reactor based* ^{99m}Mo. T*he most promising technology for the provision of* ^{99m}*Tc in the UK is its direct production by proto cyclotron bombardment. However, existing UK cyclotrons are not powerful enough for such production, and any material produced would need to be licensed before use.*[12]

Response Word Count: 530

6. What are the implications for medical research and development, including for the timely patient access to new medicines, technologies and other relevant medical innovations developed within or outside the U.K? How can any adverse consequences be avoided or mitigated and any potential opportunities be enhanced?

The UK currently enjoys access to research funding from the EU and the UK should negotiate continued access to funding or provide equivalent replacement funding for research so that patients have access to the best care in the future.

Patients can access Europe-wide trials of new treatments, particularly for rare conditions. Projects funded by the EU have enrolled over 340,000 patients[13] to clinical trials so far[14] with the UK being one of the leaders in Europe for conducting clinical trials.[15] The UK's exit from the EU must not impact patients' ability to participate in high quality research, 89% of people said that they would be willing to participate in a clinical trial if diagnosed with a condition.[16] National medical regulation can take longer than cooperative regulation (6-12 months longer for new drugs to reach Canada and Australia than the UK)[17].

In addition, time to reimbursement is seen as a major rate limiting factor when it comes to patients accessing novel therapeutic agents, particularly for orphan diseases or in oncology where cost of drug is high.

In orphan diseases, there are significant challenges around compassionate access for medicines pre- and post-marketing authorisation and while awaiting NICE approval. Current NHS processes for Individual Patient Funding Requests or Clinically Critically Urgent funding requests are inadequate and the majority of requests are declined, putting the onus on pharmaceutical companies to supply drugs free of charge. Major clinical centres are now questioning whether they should participate in global clinical studies at phase II and phase III if there is no guarantee of NHS funding post-study and if reimbursement timelines become prohibitively long. This will have a significant impact on patients

[11] B Lee, Securing a Sustainable Supply of Medical Isotopes for the UK, Nuclear Innovation and Research Advisory Board Oct 2014
[12] Future Supply of Medical Radioisotopes for the UK, British Nuclear Medicine Society and the Science and Technology Facilities Council, 2014
[13] 'What implications could Brexit have for NHS patients?', NHS Confederation, July 2016
[14] 'What implications could Brexit have for NHS patients?', NHS Confederation, July 2016
[15] 'Patient access to medical innovation under threat from Brexit' ABPI, May 2016
[16] *What do people think about clinical research?,* National Institute for Health Research Clinical Research Network, 2014
[17] 'How to secure the best for life sciences after Brexit: five key areas', AMRC, 2016

with rare or serious, life-threatening disease for whom novel therapies might otherwise be transformational.

The development of medical devices and diagnostics is also very important and coordination with veterinary medicine, particularly in the area of antibiotics, is also vital. There are opportunities to modify and improve the ability to do research, for instance by making academic research more compliant with Good Clinical Practice.

Recommendations:

- *Develop reimbursement pathways which allow for early, paid for access to medicines thereby ensuring UK is seen as an early adopter for new medical technologies.*
- *Create 'conditional' funding pathways for novel therapies with significant potential for transformational change allowing for early access and additional clinical data collection; this will require the pharma company to have a creative pricing approach pre-MAA whilst also allowing for agreed funding post-MAA if the clinical data are supportive.*
- *Ensure UK clinical trials approvals, including regulatory and ethics approvals, are done via rapid approval pathways. Keep costs of approvals competitive with other EU and global markets and ensure costs to deliver clinical trials in UK do not become prohibitively expensive, leading pharmaceutical companies to go to cheaper developing markets to conduct clinical trials.*

Response Word Count: 534

Total Word Count for Responses: 3147