

## House of Commons Health Select Committee – Brexit and medicines, medical devices and substances of human origin 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 Dr Andrew Goddard, Registrar, 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 through the Medicines and Healthcare Products Regulatory Agency (MHRA), the NHS, National Institute for health and Care Excellence (NICE), internationally renowned academic centres and multinational pharmaceutical companies. The MHRA has always played a leading role within the European Medicines Agency (EMA) since the EMA's creation in 1995 and led on approximately 20% of all of the EMA's activities during 2016<sup>1</sup>, the largest contribution of any of the European national medicines agencies.

The UK market for prescription medicines and devices comprises about 10% of the total market for prescription medicines in Europe<sup>2</sup>. Following Brexit, there is a risk that pharmaceutical companies may have less incentive to prioritise the UK as a key market for early filing and approval. In addition, several international companies have established their European headquarters in the UK because of access to the EMA in London and the single market. It is highly likely that these companies will relocate, most probably based on the new location of the EMA. Companies may also prefer to conduct clinical trials within the EU27 and will subsequently submit their marketing authorisation applications (MAAs) to the EMA. 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 could be delayed.

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<sup>1</sup> EMA Annual Report, 2016

<sup>2</sup> European Federation of Pharmaceutical Industries and Associations, "The Pharmaceutical Industry in Figures: Key Data 2016", pp. 7, 15. The size of the UK pharmaceutical market is based on sales at ex-factory prices in 2014.

Ultimately, patients may see a significant delay in being able to access new therapies and new medical technologies.

In relation to healthcare services, the UK is a net beneficiary for research grants and one of the most successful countries at securing funding from the EC. The EU research and innovation budget for 2014-2020 is around €120bn<sup>3</sup>. A lack of access to 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 EU have enrolled over 340,000 patients<sup>4</sup> to clinical trials so far<sup>5</sup> with the UK leading the way in Europe for conducting clinical trials.<sup>6</sup>

**Recommendations:**

- *The UK must maintain a system, closely aligned to the EMA, for rapid review and approval of trials and novel medicines, so that it remains a key country for the conduct of clinical research*
- *Clinicians must continue to be developed as clinical trial investigators, with the appropriate training and supports*
- *Costs for approval and delivery of clinical trials must be kept competitive, so companies are incentivised to come to the UK and use the data generated here for global regulatory filings*
- *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*
- *Focus on innovative adaptive licensing processes with a closer alignment of the regulator and health technology assessments*
- *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*

**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 continuing a close collaboration within the EU regulatory system as was set out in the statement made by Mr Jeremy Hunt and Mr Greg Clarke in July 2017<sup>7</sup>, which received support from the AoMRC<sup>8</sup>, the ABPI<sup>9</sup> and in a joint trade association letter<sup>10</sup>. However, in the situation that the UK is not able to continue to have a close relationship with the EMA and the UK adopts a separate regulatory pathway, then this must be considered a primary pathway for review, aligned to the timings for EMA review, or even as a more rapid pathway to obtain marketing authorisation. The MHRA could also 'recognise' marketing approvals by the EMA and only 'not recognise' an approval if

<sup>3</sup> ['Overview of EU funds for research and innovation'](#), EU Parliament, September 2015

<sup>4</sup> ['What implications could Brexit have for NHS patients?'](#), NHS Confederation, July 2016

<sup>5</sup> ['What implications could Brexit have for NHS patients?'](#), NHS Confederation, July 2016

<sup>6</sup> ['Patient access to medical innovation under threat from Brexit'](#) ABPI, May 2016

<sup>7</sup> <https://www.ft.com/content/e3e9ac6a-5f2d-11e7-8814-0ac7eb84e5f1?mhq5j=e6>

<sup>8</sup> [http://www.aomrc.org.uk/wp-content/uploads/2017/08/2017-07-26\\_Brexit.pdf](http://www.aomrc.org.uk/wp-content/uploads/2017/08/2017-07-26_Brexit.pdf)

<sup>9</sup> <http://www.abpi.org.uk/media-centre/newsreleases/2017/Pages/Pharmaceutical-industry-respond-to-joint-letter-from-Jeremy-Hunt-and-Greg-Clark-in-the-Financial-Times.aspx>

<sup>10</sup> <https://www.efpia.eu/news-events/the-efpia-view/statements-press-releases/13-july-2017-joint-trade-association-letter-on-brexit/>

they believe that there are strong safety or efficacy reasons to do so, that could impact patients. In addition, a separate regulatory pathway in the UK could be aligned with the reimbursement decision-making process, given that this is seen as a significant rate-limiting step to patient access, particularly for orphan diseases.

Regardless of future arrangements with the EU, the UK must continue to play a full part in major international organisations relating to medicines regulation, for example the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). ICH is unique in bringing together the regulatory authorities and pharmaceutical industry to discuss scientific and technical aspects of drug registration. Currently the UK is represented at ICH by the EMA and in any event the UK must continue to be an important contributor to any changes in these regulations with a seat at the table.

If the MHRA accept the same regulatory dossiers for product approval that are also submitted directly to the EMA, then this will reduce some anxiety of companies 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 processes and timelines.

**Recommendations:**

- *The UK should seek to continuing a close collaboration within the EU regulatory system as was set out in the letter of July 2017*
- *The MHRA should have representation at the ICH to contribute to the setting of policy and standards for medicines regulation*
- *The MHRA must be adequately resourced to perform rapid review of marketing authorisation applications for novel therapies, and be able to set a fee level that 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.*

**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?**

It is important that before March 2019 an agreement in principle is in place between the UK and the EU regarding the regulation of medicines and medical devices. 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, 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.

The medical device and the in-vitro diagnostic sectors are currently being impacted by the 3 and 5-year implementation phases that have just begun in relation to the revised European regulations<sup>11</sup>, and straddle the end of March 2019 date. It therefore seems likely that the overall implementation of these revised regulations may need a longer transition period if they are to be followed by both the UK and the EU.

There are some key roles that individuals undertake which are closely linked to the execution of regulatory procedures. 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 an EU country if they want to continue working in these defined roles. Given that approximately one-third of all the EU QPPVs currently reside in the UK it is unrealistic to expect them, and QPs, to relocate in such a short space of time.

One other concern is that of the supply chain for medicines that are currently manufactured across the EU and then imported into specific countries as required under free trade agreements. Suddenly stopping the movement of medicines would have important public health consequences for both the UK and the remaining EU 27 countries. To help with this matter a suggested 3 to 5-year implementation period may be required.

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

***Recommendation:***

- *An agreement in principle between the UK and the EU should be in place before the end of March 2019 regarding the regulation of medicines and medical devices*
- *In the interests of patient safety a transition period of around two years post-29 March 2019 would be advisable to allow any new procedures to be implemented.*
- *A transition period of 3 to 5 years may be required in relation to the supply chain for medicines*

**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. 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 should negotiate continued access to funding from the EU research and innovation budget, or provide equivalent replacement funding long-term for research so that patients have access to the

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<sup>11</sup> REGULATION (EU) 2017/745 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC

best care in the future. The Chancellors announcement<sup>12</sup> of additional research and innovation funding is welcome but it is 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 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.

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. Sharing data for Europe-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<sup>13</sup>. Without a clear data sharing framework, the UK's influence would be greatly reduced and patient safety is put at risk.

## 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 (<sup>99m</sup>Mo) from which technetium-99m (<sup>99m</sup>Tc), the most commonly used radioisotope, is derived. <sup>99m</sup>Tc is used in 700,000 medical procedures each year.<sup>14</sup> Global demand for <sup>99m</sup>Mo is growing by 0.5% a year<sup>15</sup>

The European Atomic Energy Community (Euratom) supports the secure and safe supply and use of medical radioisotopes <sup>16</sup> The UK will be required to withdraw from Euratom when we leave the EU. Ensuring a seamless continuing supply of radioisotopes must form a key part of Brexit negotiations. The UK should remain part of Euratom during any transition period.

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<sup>12</sup> <https://www.gov.uk/government/news/chancellor-philip-hammond-guarantees-eu-funding-beyond-date-uk-leaves-the-eu>

<sup>13</sup> 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.

<sup>14</sup> Future Supply of Medical Radioisotopes for the UK, British Nuclear Medicine Society and the Science and Technology Facilities Council, 2014

<sup>15</sup> 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>

<sup>16</sup> [Mission Statement](#) Euratom supply agency

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,  $^{99m}\text{Mo}$  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.<sup>17</sup>

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. A national strategy on the use of radioisotopes across the UK must be implemented, which should 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.

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<sup>18</sup>, so would require investment from the Government or industry.

**Recommendation:**

- *The UK should consider diversifying its strategy of reliance on reactor-based  $^{99m}\text{Mo}$  and support the development of non-reactor based  $^{99m}\text{Mo}$ . The most promising technology for the provision of  $^{99m}\text{Tc}$  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.<sup>19</sup>*

**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?**

Patients can currently access Europe-wide trials of new treatments, particularly for rare conditions. The UK's exit from the EU must not impact patients' ability to participate in high quality research – indeed 89% of people said that they would be willing to participate in a clinical trial if diagnosed with a condition.<sup>20</sup> National medical regulation can take longer than cooperative regulation (6-12 months longer for new drugs to reach Canada and Australia than the UK)<sup>21</sup>.

In orphan diseases, there are significant challenges around compassionate access for medicines pre- and post-marketing authorisation and while awaiting NICE reimbursement 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

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<sup>17</sup> [http://www.world-nuclear-news.org/np\\_isotope\\_supply\\_further\\_tightened\\_by\\_transport\\_restrictions\\_0110081.html](http://www.world-nuclear-news.org/np_isotope_supply_further_tightened_by_transport_restrictions_0110081.html)

<sup>18</sup> B Lee, Securing a Sustainable Supply of Medical Isotopes for the UK, Nuclear Innovation and Research Advisory Board Oct 2014

<sup>19</sup> Future Supply of Medical Radioisotopes for the UK, British Nuclear Medicine Society and the Science and Technology Facilities Council, 2014

<sup>20</sup> [What do people think about clinical research?](#), National Institute for Health Research Clinical Research Network, 2014

<sup>21</sup> [How to secure the best for life sciences after Brexit: five key areas](#), AMRC, 2016

impact on patients with rare or serious, life-threatening disease for whom novel therapies might 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.

**Recommendations:**

- *Develop reimbursement pathways through the evolution of schemes such as the Early Access to Medicines Scheme (EAMS) which allow for early, paid-for access to medicines, ensuring the UK is seen as an early adopter*
- *Create 'conditional' funding pathways, allowing for early access and additional clinical data collection, for novel therapies with significant potential for transformational change. This will require pharmaceutical companies 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 and keep costs of approval competitive*