



## Brexit and the impact on patient access to medicines and medical technologies

The UK's plans to leave the European Union (EU) and the EU's single market could have serious implications for patients' access to medicines and medical technologies. This briefing explores how UK and EU citizens could be affected by the disruption in trade that could result from the UK's exit from the EU, as well as in the event of lack of cooperation in the regulation of medicines and devices between the EU and the UK post Brexit.

### Summary

- The regulation of medicines and medical technologies is managed by EU-wide systems, facilitating trade under the single market. This means that products are regulated to make sure that they are safe before they can be placed on the EU market. They are also closely monitored after being placed on the market to ensure continued safety.
- The regulatory arrangements for medicines and medical devices are complex and changes to this regime may have an impact on supplies across Europe. 'No deal' or a deal between the UK and the EU that does not address future cooperation on medicines and medical technologies could put public health at risk.
- As the EU and the UK are making plans to move to phase two of the Article 50 negotiations, which looks at the future relationship between the EU and the UK, it is critical that arrangements for the regulation of medicines and medical devices should be addressed as a matter of urgency.

### What the Brexit Health Alliance is calling for:

- No negative impact on patients. Future cooperation on medical devices and medicines to be prioritised in the negotiations, so that patients and the wider public are not negatively impacted from disruptions in the supply of medicines and other health technologies, or from a reduction in standards or safety.
- Patient safety and public health to be guaranteed post Brexit through aligning the UK as much as possible with the EU's regulation of medicines and medical devices, and by close regulatory cooperation between the EU and UK, as proposed by the UK government.<sup>1</sup>
- Pragmatic solutions allowing patients and the public to benefit from the UK's participation in EU systems such as data sharing networks, pharmacovigilance and the new clinical trials infrastructures post Brexit.
- An implementation period beyond the two years of Article 50 negotiations (which end in March 2019). This period should adequately reflect the time needed to ensure relevant customs, trade and regulatory procedures are in place.

# How has EU regulation on medicines and medical technologies benefited patients?

The primary benefit of a harmonised EU regulation for medicines and medical technologies is that patients *are guaranteed a high level of safety*. All medicines and medical products on the EU market must be of a high standard, and most importantly, proven to be safe and efficacious (or performing as intended in the case of devices) before they can be placed on the market in the EU. This means that almost 500 million people in the EU benefit from these high standards, whilst also encouraging companies to research and develop medicines in the EU.

The EU has also developed robust mechanisms for continued surveillance of products already on the market to ensure that they are safe. Patients benefit when countries can work together to map out adverse events, as it is easier to define trends and problems with more data and larger populations.

For medical technologies, National Competent Authority Report exchange (NCAR) is the process whereby competent authorities such as the UK's Medicines and Healthcare Products Regulatory Agency (MHRA) disseminate vigilance data. Vigilance is thus a Europe-wide activity helping to ensure patient safety and consistency of actions across member states. Since 2012, there have been 4,785 NCARs across the EU.<sup>2</sup>

For medicines, this surveillance is called pharmacovigilance. The Pharmacovigilance Risk Assessment Committee (PRAC), established in 2013, plays a crucial role as a signalling system and makes recommendations on the management of these.<sup>3</sup> For example, recommendations can include restrictions on use and advice on optimal use of medicines. This has been able to deliver more timely decision-making and to conduct major public health reviews on available medicines.

Shared regulatory frameworks at EU level have been crucial in providing patients with faster access to treatments. In the global market, separate national systems of regulation of health technologies can slow down treatments for patients. This applies particularly to smaller patient groups which is why regulatory oversight across the EU brings particular added value for children and rare disease patients.

For children, the 2006 EU Paediatric Regulation<sup>4</sup> aims to promote high-quality research into the development of medicines for children. Specifically, it is designed to make sure that over time, most medicines used by children are tested and authorised for such use. It has the dual aim of obliging and incentivising industry to conduct paediatric clinical trials. It has certainly contributed to increased research in medicines for children in the EU with the number of children in registered clinical trials jumping from 3,648 to 211,302 in the period 2006–2015. This 60-fold (6,000 per cent) increase represents a very significant growth in research about children funded by the pharmaceutical industry.<sup>5</sup>

For rare disease patients, the EU regulation on orphan medicines<sup>6</sup> has incentivised the development of products intended for the diagnosis, prevention or treatment of life-threatening or very serious rare conditions. Taken together, between 6,000 and 8,000 rare diseases affect the daily lives of around 30 million people in the EU. To date the EU has authorised 141 orphan medicines, and designated 1,508 products as orphan medicines.

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# What is at risk if no solution for medicines and medical devices is found?

**Certain medicines and medical technologies may be delayed in reaching patients or may even become unavailable to patients if no solution for medicines and medical devices is found during the Brexit negotiations.**

## Access to new medicines and medical technologies

As a result of the relocation of the European Medicines Agency (EMA) to Amsterdam, the agency had to de-prioritise certain activities, such as its work on paediatric medicines and public health issues. This includes its work on anti-microbial resistance and flu pandemics. While expertise will be developed over time, the loss of the UK's national competent authority, the MHRA, to the joint pool of expertise available under the EMA could be detrimental to the scientific approval of medicines for the EU market in the interim. In 2016, the MHRA led 20 per cent of scientific evaluations of new medicines for the EMA.

As for medical devices, it is estimated that around 50 per cent of the assessment work needed for the authorisation of products to be placed on the EU market takes place in the UK. There is already limited capacity in this area across Europe and any possible loss of capacity could clearly impact the availability of medical devices.

At a time when there are more new medicines and medical devices than ever coming on the market, it would be regrettable for European patients to face delays in accessing new medicines due to delays in the European approval pipeline as companies launch their products first in Asia and the US.

There could also be additional delays for UK patients in accessing new medicines, as the experience of Switzerland, which is not a member of the EMA, shows. Despite having a number of bilateral trade agreements with the EU, it is estimated that Switzerland gains access to new medicines on average 157 days later than the EU.<sup>7</sup> In Australia and Canada new medicines come to market on average 6–12 months later than in the EU or USA. The EMA currently represents 25 per cent of the global pharmaceutical sales market, compared to the UK's 3 per cent share.<sup>8</sup>

Additionally, a recent report by the Office of Health Economics<sup>9</sup> (OHE) outlines the potential for delay in submissions of new marketing authorisations after the UK leaves the EU. The report states that depending on the final outcome of the negotiations the potential impact on the UK means:

- the average lag of submission could be 2–3 months
- five–15 per cent of applications could be submitted more than a year after the EU27/EEA submission
- some products may never be marketed in the UK – 45 per cent of applications had not been submitted to any of the three reference countries (Australia, Canada, and Switzerland) following submission to the EMA at the time of the OHE analysis.

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## Supply of medicines and medical technologies

Decades of cooperation and harmonisation of standards on medicines and medical technologies have led to the growth in frictionless trade and supply of goods and products across the EU's single market and customs union. The scale of trade between the UK and the EU is substantial, delivering medicines and medical devices to patients in the UK and the EU. For medicines, 45 million patient packs go to the EU from the UK every month, and 37 million patient packs go from the EU to the UK. Products are often developed in complex supply chains from across Europe. Any divergence from these harmonised standards by the UK in the future, and a lack of agreement on cooperation with the EU on medicines and medical devices, would mean that supply chains are at risk.

Marketing authorisations for medicines held by a UK company will no longer be valid to legally supply medicines into the EU post-March 2019 and vice versa, unless this is specifically agreed upon in the Brexit negotiations. There are currently approximately 2,400 licences or around 361 products (37 per cent) for which the centrally marketing authorisation procedure is held by UK-based companies. These licences will need to be reviewed in order for the products to be made available to EU patients in case a system of mutual recognition is not agreed between the UK and the EU in this area.<sup>10</sup> Conversely, where licences are held in the EU, there will be potential disruption in the UK. This means that a solution will have to be found for the approval of 978 medicines on the UK market that have received marketing authorisation via the centralised European procedure since 1995.<sup>11</sup>

There could also be problems with the supply of medical devices in case a system of mutual recognition is not agreed between the UK and the EU. Several UK manufacturers use EU-based warehousing and distribution centres, particularly for high-volume consumables. Moreover, manufacturers from outside the EU have appointed in the region of 55 per cent of all authorised representatives in the UK. UK-based notified bodies perform around 50 per cent of all conformity assessment activities for medical devices placed on the EU market.

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# Case studies showing potential impact on patients access to medicines and medical devices

## **Availability of medicines for prostate cancer patients**

Developed in the UK, and manufactured in the UK since 1987, this treatment is used for prostate cancer and in the treatment of breast cancer. It is a global product which is manufactured only in the UK and is marketed in over 80 countries.

This product is both manufactured and quality control tested at the same site. State of the art, sterile, manufacturing facilities have been built and investment continues to support both the manufacture of this highly complex product and the testing laboratories, equipment and skilled staff required to assure product quality.

Over 350 people are involved in the manufacture, testing and quality release of the product. The low turnover, long-service workforce has developed and retained the technical capability required to ensure the on-time release of this treatment to meet the needs of patients in over 80 markets. The medicine is formulated and manufactured in eight major processes during the processing stage, and eight major processes in the primary packing stage. Total manufacture lead time is 12 months from active pharmaceutical ingredient (API) production to finished pack release.

## **Impact on patients**

- Faced by the possibility of a no deal Brexit scenario, the manufacturer has begun planning the duplication of quality testing and release facilities in an EU27 location.
- However, the calculated duplication time for the manufacture and quality control testing is at least 42 months, with a risk of taking longer. This would affect the supply of this cancer treatment to patients, including up to 120, 000 in Europe each year.
- Due to the technical complexity of the analytical methodology and specific equipment required, it will be extremely challenging to transfer such knowledge from the UK to testing laboratory within the EU27 by April 2019.

The possibility of disruption to supply would be avoided through a continued agreement and mutual recognition on testing between the UK and EU. Alternatively a suitable transition period and a future relationship between the UK and EU that maintains alignment on medicines regulation and trade would reduce the risk of complete supply disruption.

## **Future of European clinical trials jeopardised**

There are currently 1,500 registered clinical trials including multiple EU member states with a UK sponsor (lead). Fifty per cent of those trials will be ongoing as of March 2019. After March 2019, the continuing conduct of these trials could be jeopardised due to the lack of the same regulatory framework or to the lack of the UK's access to the new EU infrastructure for the management and authorisation of clinical trials.

### **Customs checks could cause delays to care and treatment of critically injured during emergencies**

Accident and emergency trauma packs (which are full of equipment and medicines) are flown in from the EU to the UK within hours from the order being placed to the operating room (OR) in a hospital. This short time frame is particularly necessary during unexpected large-scale emergencies, such as terrorist attacks, when a large number of people are suddenly seriously injured. Hospitals do not always stock pile these packs on a large enough scale to deal with these extreme emergencies because the medicines and devices included in them would risk running past their product shelf life and many packs would be wasted.

It is anticipated that post-Brexit customs checks could result, in one of the best-case scenarios, in a delay of five hours.\* These five hours are critical in life and death situations where critically injured patients need care and treatment as soon as possible.

**\*House of Commons Home Affairs Committee (16 November 2017), *Home Office delivery of Brexit: Customs operations – First report of session 2017–19*, p15.**

### **Potential delays in access to new medicines for rare disease patients**

#### **Duchenne muscular dystrophy**

Duchenne muscular dystrophy is a severe type of muscular dystrophy for which there is no cure and limited treatment options available. At any one time, there are estimated to be 26,000 patients in the EU, and 2,500 people affected by Duchenne muscular dystrophy in the UK.

There are several promising treatments progressing through the clinical trials process and a number of these are awaiting authorisation by the EMA. One particular drug could be assessed by the EMA in the next few years. If successful, these medicines could effectively slow down the progression of the condition and result in significant benefits to those affected.

Without a UK link to the EMA's medicines approvals process, and considering the small population size and market opportunity for pharmaceutical industries, individuals with Duchenne muscular dystrophy in the UK could face lengthy delays in accessing the medicine compared with patients with the same condition living in EU countries.

### **Certain medical devices may not be available to patients**

Medical devices rely on international supply chains, both for finished products and product components. For global companies in particular, this comes from competitive, intra-company bidding to determine which of their international manufacturing sites is best placed to produce particular products within the company's portfolio. Components are subsequently sourced as appropriate, usually from across Europe and beyond, and finished goods are then exported globally.

This often means that the company's entire global inventory is manufactured in one place. Needles and tubes for blood collection manufactured in very high volumes in South West England serve all of Europe, whilst an international company which manufactures orthopaedic implants, produces certain of its products for the rest of the world in South Wales.

### **Threats to public health – disruption in monitoring of products to ensure patient safety**

The MHRA contributes to up to a third of the EU's pharmacovigilance work. Similarly, in 2016, the UK alone contributed 23.4 per cent of all national competent authority reports (NCARs) submitted to EU members, demonstrating that the UK is a significant partner in the continued health of both UK and EU patients.

In addition to formal vigilance activities, the MHRA are significant partners in the Joint Assessment Programme (JAP) coordinated by the European Commission. The JAP aims at the re-designation of notified bodies against the Medical Device Directive (and in future the Medical Device Regulation), to ensure that notified bodies' performance and competence are uniform and at a consistently high level. Of the 59 joint assessments since the inception of the JAP in December 2013, the MHRA have contributed 11 of the 63 experts within the process, ranking second behind Ireland, who contributed 13 during the same period. Eleven experts therefore represent 17 per cent of the European resource. It is also important to note that the chosen language for these assessments is English.

The loss of data from a country that has a large population (the UK) and the valued reporting capacity of the MHRA would have an impact on the effectiveness of safety reporting across the EU, but also the loss of access to European data and reporting would clearly impact the UK's ability to map trends in safety of devices and medicines.

The Office of Health Economics has warned of delays of up to five months in signal detection and management for pharmacovigilance in the UK and the EU27/EEA.

### **Chemotherapy patients and people suffering from epilepsy are left without the right treatment**

Eisai manufactures chemotherapy and anti-epileptic medicines at their Hatfield headquarters in Hertfordshire. This is a highly specialised manufacturing plant, requiring unique technical and scientific infrastructure to allow the necessary testing to take place. Various ingredients for these are processed in other states and imported from the EU into the UK for completion. The finished products are then packaged and exported to other EU member states and all over the world. Production of pharmaceuticals often involves multiple cross-border transfers between the UK and EU countries.

Eisai is currently looking to potentially move the testing facility outside of the UK to Europe due to the risk of there being no agreement, where patients on both sides of the channel risk not having access to medicines to treat their life-threatening conditions.

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# Background note: How are medicines and medical devices regulated across the EU?

## Medicines

In 1965, on the back of the thalidomide tragedy, the EU decided that medicines needed to be authorised before being sold on the EU market, and went on to develop structured medical regulations.

Over the past 50 years, the regulatory landscape has dramatically evolved. In 1995, the EU initiated a centralised Europe-wide procedure for the authorisation of medicines, which includes a European agency (the European Medicines Agency) responsible for joint scientific evaluations and authorisations.

The EMA works with a network of national authorities, including the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK. Authorisations are given for medicines to be manufactured and supplied within Europe and the medicines and their manufacturers are continuously monitored to ensure quality and safety standards are being met.

The majority of the scientific assessments are conducted by relevant authorities from EU member states, such as the MHRA, so resources and expertise across Europe are pooled. The EU has defined guidance on good manufacturing practices (GMPs), guidelines which govern the production, distribution and supply of a medicine, to guarantee the highest standards of efficacy, quality and safety of products. In order to be made available to patients in the EU, batches of medicines must be tested and then released by a qualified person located in the EU. There are more stringent, supplementary checks by an independent agency for biological medicines, including vaccines, before they can be placed on the market.

The EU also has legislation on the conduct of clinical trials in the EU, as well as laws to increase the number of products for rare diseases and medicines for children. Alongside this, there have been new EU rules and mechanisms to strengthen the system for safety of medicines (known as pharmacovigilance) which tackles issues such as detection and assessment of adverse reactions to medicines and direct patient reporting of adverse events. Rules have also been created to protect patients from the risk of

falsified (counterfeit) medicines. Additionally, the EU also has legislation on advanced therapy medicines, that are based on novel treatments, including gene therapy, cell therapy and tissue engineering.

## Medical technologies (medical devices and in-vitro diagnostic (IVD) devices)

The medical devices and in-vitro diagnostics industries are regulated by national competent authorities, such as the UK's Medicines and Healthcare Products Regulatory Agency (the MHRA). These competent authorities subsequently, due to the high volumes and variation of devices and IVDs to be regulated, contract the processes of auditing 'conformity assessment' and 'product compliance' to private sector organisations called 'notified bodies'. Dependent on the risk presented to the patient by the product, a notified body will attest to compliance allowing the manufacturer to affix a CE mark, meaning that the device can be made available for use on the EU market. In addition to this initial compliance task, manufacturers are obliged to conduct, again according to presented patient risk, regimented post-market surveillance activities, to monitor product performance against quoted indications for use.

EU law specifies the essential requirements that products must fulfil in order to be placed on the EU market. This involves a procedure for assessment of conformity (both for quality management and product based), which includes demonstration of design and development, product safety, clinical performance, manufacturing consistency, post-market surveillance and for packaging and labelling. The new regulations for medical devices and IVDs published in May 2017 with three- and five-year transition periods respectively, ensure that the legislation is in line with technological advances.



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## What the Brexit Health Alliance is calling for

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- An implementation period beyond the two years of Article 50 negotiations (which end in March 2019). This period should adequately reflect the time needed to ensure relevant customs, trade and regulatory procedures are in place.

## Brexit Health Alliance members

Co-chairs: Niall Dickson CBE, Sir Hugh Taylor

Secretary: Kate Ling

Members: Academy of Medical Royal Colleges, Association of Medical Research Charities, Association of British Healthcare Industries, Association of the British Pharmaceutical Industry, Association of UK University Hospitals, BioIndustry Association Faculty of Public Health, Medical Schools Council National Voices, NHS Confederation (including Mental Health Network, NHS Clinical Commissioners, NHS Employers, NHS Partners Network), NHS Providers, Northern Ireland Confederation for Health and Social Care, Richmond Group of Charities, Scottish NHS Chief Executive Group, Welsh NHS Confederation.