BMJ 2018;363:k4724 doi: 10.1136/bmj.k4724 (Published 14 November 2018)

FEATURE

Braced for Brexit

Availability of drugs—including blood products, insulin, and nuclear medicines—and treatment of rare diseases are some of the areas where uncertainty caused by UK-EU negotiations is increasingly concerning doctors, suppliers, and patients

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Blood and insulin: a cold storage catastrophe?—Nigel Hawkes and Jacqui Wise

If the UK leaves the European Union without a deal in place, supplies of drugs could face "a catastrophic time," according to Martin Sawer, executive director of the Healthcare Distribution Association.

Two types at particular risk are insulin and biological medicines, including those derived from blood plasma—because the UK relies on imported supplies. The six week buffer stock that health secretary Matt Hancock has asked drug companies to set up in case of short term border disruption is straightforward (if costly) for drugs with a long shelf life. It is trickier for those that need to be kept at a controlled, low temperature during transport and storage.

Mike Thompson, chief executive of the Association of the British Pharmaceutical Industry, told the Commons select committee no deal Brexit inquiry on 23 October[1] that the government's contingency plans were insufficient. There were no cold chain storage facilities at the ports in the event of delays and not enough medical cold stores generally in the UK, he said. "I think we've got to the stage of recognising that stockpiling won't be enough and we need to put in the next phase of plans."

In a last minute effort to close the gap, the Department of Health has issued tenders for additional cold storage—either newly built or, more likely, converted from facilities designed to store food. "I am confident this can be delivered by March next year when the UK leaves the EU," Hancock told the committee. Others, including Thompson and Sawer, are not so sure. Sawer doubts there is now time to build new cold storage, which typically takes a year, but renting capacity from the food industry might suffice.

He is worried that some of the UK's 2000 companies that hold a wholesaler's licence might exploit the situation by buying up stock and not releasing it to the market, creating shortages and raising prices. He wants the government to take emergency powers to control the market, but Hancock told the committee he was not considering emergency powers and insisted that supplies should be maintained even with a no deal.

Hancock has written to NHS Trusts, pharmacies, and GPs warning them not to stockpile drugs or write longer prescriptions for patients in the weeks leading up to Brexit.[2 3] However, Sawer told the committee that patients might need to ensure they had their own stocks. "We're not suggesting anyone needs to stockpile outside of the supply chain yet, but come January that might be a different picture," he said. "I'm not pulling any punches."

Necessary for survival

People with diabetes are among those who have expressed worry on social media, including talking about stockpiling their own supplies. Nikki Joule, policy manager at the charity Diabetes UK, tells *The BMJ*: "We are concerned that government hasn't communicated its plans regarding the continued supply of insulin in the event of a no deal Brexit, which is causing unnecessary concern for people with diabetes."

Her colleague Libby Dowling, the charity's senior clinical adviser, adds: "For people with type 1 diabetes, and for some with type 2 diabetes, insulin isn't a luxury; it's necessary for survival."

Diabetes UK estimates that 1.14 million people in the UK rely on insulin. Only one company makes insulin in the UK: Wockhardt UK. But this produces porcine and bovine insulin, which only about 1500 to 2000 patients use. Most people with diabetes use analogues or synthetic human insulin. All of this is imported, mainly from three main manufacturers—Lilly, Sanofi, and Novo Nordisk.

Sawer told the select committee that the government's basis for stockpiling an additional six weeks' supply of medicines to prepare for no deal has not been explained to companies. Insulin suppliers are already building up stocks further than this. Novo Nordisk confirmed to *The BMJ* that it is increasing UK stocks to about 16 weeks from the final quarter of this year—double its current stock level.

Sanofi says it will hold a 14 week stockpile. Lilly will not release any figures but a spokesperson says the company "is

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working to plan for a worst case 'hard Brexit' in March 2019 and we have undertaken comprehensive analysis of the risks that would pose to our business, and critically, our ability to supply medicines in the UK." The spokesperson adds: "We continue to urge government to maintain regulatory cooperation with the EU to prevent the burden of duplicative regulation and testing that could slow the complex supply chain."

WHO essential medicines

Also at risk are a range of products derived from blood plasma, including albumin and immunoglobulins. (Blood for transfusion is not a problem since the UK is close to self sufficient, and clotting factors for haemophilia and von Willebrand disease are now made by genetic engineering using recombinant DNA methods.)

Plasma products are the outcome of a complex supply chain beginning, more often than not, in the US. Blood donations there are paid for, generating a surplus. The resulting plasma is then shipped around the world to factories where it is "fractionated" into a range of products. Globally, the business is worth about $20bn (£15bn; €18bn) a year.[4]

The UK has one such fractionating plant, run by the BPL Group in Elstree, Hertfordshire. David Lewis of BPL says that the company supplies about 40% of the UK's albumin needs and is "a small player" in immunoglobulins. All other plasma products are supplied by companies outside the UK, including CSL Behring (US), Shire l (Ireland), Grifols (Spain), Biotest (Germany), and Octapharma (Switzerland).

Susan Walsh, director of the patient organisation Primary Immunodeficiency UK, says she has "grave concerns" about post-Brexit supplies of immunoglobulins. "The supply is necessarily heavily regulated and therefore at risk of disruption during the transfer to a new regulatory system," she says.

"There has been increasing difficulty in sourcing immunoglobulins, and supplies are limited with little opportunity or available facility to stockpile. Human immunoglobulin is the only treatment option available for some patients to prevent life threatening infection and is a WHO listed essential medicine for patients affected by PID."

"We need a fast track route"

The immediate danger for people with diabetes and primary immunodeficiency is that imports will delayed at the ports in the transition period after a no deal Brexit; hence Hancock's call for a six week stockpile and more refrigerated warehouses in which to store it.

Thompson says that 90% of medicines imported from Europe pass through Dover or Folkestone, where delays are likely to be acute. The government is considering using other ports and possibly airfreight. Hancock told the select committee that this option was more likely for short half life radioisotopes (see below) than for medicines.

Thompson says: "We need a fast track route. Airlifting is a possibility as we already use that for drugs for clinical trials, but in a no deal scenario lots of people will want airlifting so there's a question of capacity. Another alternative might be sourcing products from the US or India."

Delays to new treatments

There are potential longer term concerns for patients depending on the type of Brexit. The BMA, the drug industry, and the Brexit Health Alliance have all warned that if the UK develops a divergent approach to licensing from the European Medicines Agency it could lead to delayed access to new medicines and medical devices.

Niall Dickson, co-chair of the Brexit Health Alliance, says: "We know that countries outside the European Medicines Agency can experience delays. Switzerland, despite a bilateral trade agreement with the EU, experiences delays in accessing new medicines. We have to find a way of exiting the EU without disrupting access to innovative and safe medicines for patients in the UK and in Europe."

The BMA warns that a separate regulatory system for medicines could lead to delays of 12 to 24 months in accessing life saving drugs; weaker post approval regulation and pharmacovigilance because of reduced capacity to manage and detect adverse drug reactions; and loss of expertise in regulatory processes and pharmacovigilance. It is calling on the government to work closely with the EMA through a formal agreement to continue to support and participate in their assessments for approving medicines and to agree mutual recognition of and ongoing participation in the CE mark scheme.[5]

Nuclear medicine: time waits for no radioactive drug—Stephen Armstrong

When, in August, the UK government told drug companies to stockpile medicines to prepare for a no deal Brexit, the press had a field day.[6] Yet little attention was given to a stark challenge faced by patients with cancer and their clinicians: some key diagnostic tools and cancer treatments rely on radioactive isotopes that will have decayed and become effectively useless if delayed for six weeks coming into the country.

Roughly one million diagnostic nuclear medicine tests are done in the UK every year, according to the British Nuclear Medicine Society. About 150 000 of these use a radiopharmaceutical called F-18 fluorodeoxy glucose (FDG), which has a two hour half lifeso is normally made within 60 miles of the hospital where it is used. The remaining 850 000 tests need technetium-99m (^{99m}Tc), which is used in bone, cardiac, lung, and kidney scanning as well as during surgery for breast cancer.[7]

Tc-99 is produced by the radioactive decay of molybdenum-99 (^{99}Mo), which in turn is produced in nuclear reactors. Neither isotope can be stockpiled because both decay rapidly: the amount of useful radiation emitted by ^{99m}Tc halves every six hours, and the yield of ^{99m}Tc from ^{99}Mo halves every 66 hours, with unstable atoms releasing radiation to become more stable.

The UK also imports iodine-131 to treat thyroid cancer, radium-223 to treat bone tumours, and lutetium-177 to treat neuroendocrine tumours as it has no reactors capable of producing them.[8] Since the isotopes decay rapidly, UK hospitals rely on a continuous supply by lorry from reactors in France, Belgium, and the Netherlands.

The longer half life of ^{99}Mo means it can be delivered weekly, but ^{131}I has a half life of 12 hours so has to be delivered on the day, and any delays or queues at ports could result in it being unusable.

Cancer treatment

Radioisotopes used for cancer treatment are also at risk. The main radioisotope used is iridium-192. Roughly 1500 women and 2000 men each year receive treatment with implants containing iridium for cervical and prostate cancer.

Iridium's 74 day half life means that half of the radioisotope has decayed after three months.[9] "That means you're getting

half of the activity you prescribe which—in the case of cervical cancer—means the treatment takes much longer," says Jeanette Dickson, vice president for clinical oncology at the Royal College of Radiologists.

At the moment, the use and transport of radioactive material is governed by the EU's Euratom programme,[10] which the government's EU withdrawal notification said the UK intends to leave.[11] The reasons for leaving are not specified, but researchers at the Institute of Government believe that staying in Euratom would require the UK to compromise on the negotiating positions set out by the prime minister regarding the European Court of Justice, which has jurisdiction over the body.[10]

"Leaving Euratom risks breaking a series of time sensitive supply chains," says John Buscombe, president of the British Nuclear Medicine Society. "If we don't have the isotopes, the tests can't get done—because delivery is timed for the morning of an appointment patients may arrive at hospital, find we have nothing to give them and then go home and wait for another slot. A lymphoma positron emission tomography scan is timed to be just before the treatment. If you delay the scan, you affect treatment outcomes and patients may die."

Warnings from Northern Ireland

It is possible to fly radioisotopes into the UK.[12] Currently, radioisotopes bound for Northern Ireland are flown to Coventry airport, but even under the existing Euratom regime Northern Ireland faced shortages of necessary radioisotopes in 2009 and 2013 because of supply chain problems.[5]

"The problem is our supply chains are built around lorries from the Channel," explains Dickson. "It would take a substantial, expensive, and time consuming process to reorganise all those supply chains but we can't consider the process until we have a clear picture on the post-Brexit deal."

Whatever the solution, restoring a regular supply will take time and money—but until the terms of the deal are agreed no planning can take place. The NHS, clinicians, and the British Nuclear Medicine Society have been asking the government for information and solutions but the outcome is still unclear. "The civil servants we've spoken to take it seriously but they don't know what to do," Buscombe says.

Rare diseases: collaboration at risk—Tom Moberly

Some conditions are so rare that they affect just a handful of people in any one country. To grow the expertise to diagnose and treat these conditions, clinicians have developed ways of working with colleagues in other countries to share learning and knowledge, and to collaborate on research into new treatments.

For patients in the UK, these ways of working are now centred around the European Reference Networks (ERNs). These networks were set up under the EU's crossborder healthcare directives and receive funding from the EU.

Once the UK leaves the EU, it is uncertain whether the UK will still be able to collaborate in these networks. Genetic Alliance UK, a charity that works with families and patients with genetic conditions, warns that the care of UK patients will be undermined if the UK is unable to work in these networks because of Brexit.

"Losing our ability to collaborate, participate, and indeed lead those networks as a consequence of Brexit would be a really big disbenefit for patients with rare diseases and their families in the UK and across the EU," says Jayne Spink, chief executive of the charity.

"We have a structure within the EU that's been working well in terms of promoting and supporting research and clinical research for rare diseases for a number of years. The majority of touch points for that infrastructure are at risk or affected by Brexit."

A rare disease is defined as one that affects no more than one in 2000 people. Although a single rare disease might affect just a handful of people in any one country, there are thousands of known rare diseases, and many more conditions that do not represent any known disease. Every year in the UK 6000 babies are born with a syndrome without a name. In fact, around 6% of the UK population will be affected by a rare disease at some point in their lifetime.

These rare diseases tend to require a high level of expertise to be recognised, diagnosed, and treated appropriately, Spink explains. "It's difficult for any one country to provide sufficient numbers of patients, sufficient expertise, and sufficient capacity to carry out a clinical trial or to gather sufficient information about the natural course and the cause of that condition to develop effective care and treatment across someone's lifetime," she says.

To get around this problem, clinicians have relied on learning and research communities and collaborations. The European networks currently link around 20 000 healthcare professionals in 300 centres of excellence across 26 countries.

"The ERNs have virtual advisory panels and they have a dedicated IT platform and telemedicine tools," Spink explains. "It's not that patients are being shipped around—knowledge and information and things that can help with diagnosis and care are being shared."

At the moment, the UK has a central role in the ERNs. The NHS leads a quarter of the 24 networks and is involved in all but one of them. This includes 40 UK centres of excellence and 114 specialist units providing care for 150 000 patients with rare diseases in the UK.

No post Brexit commitments

How the collaborations that underpin care for these patients will continue after Brexit is not clear. "There's no guarantee, and we're not aware of solid commitments," Spink says.

"You could imagine several different scenarios. But the most desirable outcome would be for the UK to be able to continue to be a cornerstone of the ERNs. That benefits patients here,but it also benefits patients across Europe." Genetic Alliance UK is asking people to sign up to a campaign that calls on all parties to work towards a positive outcome and for continuing involvement of the UK in the ERNs.

Warning about the effect of Brexit on patients with rare diseases earlier this year, Niall Dickson, from the Brexit Health Alliance, said that the UK and its EU neighbours had come to depend on each other to advance medical research. "We want to see preserved levels of cooperation [in medical and health research] which have built up over the past 15 or 20 years, on a whole range of areas, particularly on rare diseases where some fantastic cooperation has developed,"[13] he said.

The Brexit Health Alliance also submitted written evidence to the Commons Health and Social Care Committee's ongoing inquiry into the effect of a "no deal" Brexit and health and social care.[1] The alliance said that, in the event of a no deal Brexit, NHS trusts would no longer be full members of ERNs. "The

six UK ERN coordinators have already been asked to identify and hand over their responsibilities to another member centre not in the UK," it said. "The process of NHS trusts applying for further funding to support ERNs beyond March 2019 has been suspended. ERNs are seeing a loss of leadership and jobs, as well as less access to EC funding even before Brexit occurs. This presents a risk to patients with rare diseases."

As well as affecting the sharing of knowledge, Brexit could lead to fewer treatments for rare diseases being available to UK patients, Genetic Alliance UK believes. "The thing about rare diseases is that research and care are so intimately entwined—and that's intimately entwined in decisions about developing medicines and providing access to them. It's an ecosystem," Spink says.

"If trials are not carried out here, that might have a negative impact on the decision to market and launch products here. It could be that the UK loses out because we're a late choice for launch or because companies choose not to launch at all, given that we're only 3% of the global market."

Competing interests: We have read and understood BMJ policy on declaration of interests and have no relevant interests to declare.

Provenance and peer review: Commissioned; not externally peer reviewed.

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