Brexit and the Regulation of Medicines – the Story So Far

In a previous edition of *The Journal*, I posed the question "Veterinary Medicinal Products – What Might happen if the UK Withdrew from the European Union?"[1] At the time of writing that article, the Conservative Party in the UK had promised, as part of its election manifesto for the 2015 general election, to hold a referendum to determine support for the UK either remaining as a member of the European Union (EU) or leaving. The Conservative Party did win the 2015 election and a referendum was held. The UK voted to leave the UK and Brexit, a portmanteau term for 'British exit from the European Union' became a reality.

As I noted in my previous article, UK membership of the EU had long been a topic for debate – frequently very heated debate. In fact, a previous referendum on the UK's continued membership had been held in 1975 only two years after the UK joined what was to become the EU. At that time 67.2% voted "yes" and 38.2% voted "no". The UK remained in the EU.

Following the 2015 Conservative victory, the UK Parliament passed the European Union Referendum Act 2015 and the referendum date was set for 23 June 2016. An official group, Britain Stronger in Europe, campaigned for remaining in the EU, while another official group, Vote Leave, campaigned for the opposite. The former group was endorsed by the then Prime Minister, David Cameron and the then Chancellor of the Exchequer, George Osborne, while the latter group was led by the Conservative MP Boris Johnson and the then Secretary of State for Justice, Michael Gove. Two campaigns began and this heralded several months of discussions, arguments and debate. The referendum was duly held on the appointed date, with a single question on the ballot paper:

Should the United Kingdom remain a member of the European Union or leave the European Union?

Two options were provided:

- Remain a member of the European Union
- Leave the European Union

The same question and voting options were also drafted in Welsh. Eligibility to vote was (and still is) defined by legislation as limited to residents of the UK who were Commonwealth citizens under the British Nationality Act 1948 or those who were also citizens of the Republic of Ireland, or both. Residents in the UK, including Gibraltar, who were the citizens of other EU countries were not allowed to vote unless they were citizens of the Republic of Ireland, of Malta or of the Republic of Cyprus.

Much to the surprise of everyone (well, nearly everyone), the UK voted to leave the EU. Much has been made of the overwhelming leave vote, but, as the table below shows, the majority was only 1,269,501 which admittedly sounds substantial, but amounts to only 3.8% of the votes cast.

	Votes	%
Leave	17,410,742	51.89
Remain	16,141,241	48.11
Total Invalid	25,359	0.08
Voter turnout	46,500,001	72.21

England, together with Gibraltar and Wales overwhelmingly voted 'leave' (although Gibraltar voted by a majority of 95.9% to remain), while Northern Ireland overwhelmingly voted 'remain'. All constituencies in Scotland voted 'remain'. The immediate outcome of the overall result was that David Cameron announced his intention to resign as Prime Minister and Leader of the Conservative Party the following day. On July 13, 2016, Theresa May took over from Cameron. She did not offer George Osborne a position in her new Cabinet. A new government department, the Department for Exiting the European Union, was established to oversee negotiations with the EU and establish the future relationship between the EU and the UK. Theresa May promised not to seek permanent membership of the European single market or the EU customs union after exiting the EU, and promised to repeal the UK's European Communities Act (1972).

Demographic analysis of voting patterns showed that older and less educated voters were more likely to vote leave. While a majority of white voters voted leave, only 33% of Asian voters and 27% of black voters wished to leave. Generally, voting to leave the EU was strongly associated with holding socially conservative political beliefs, opposition to cosmopolitanism and thinking that life in the UK 'is getting worse.' Support for leaving the EU was associated with opposition to immigration from other EU countries to the UK.[2]

The Aftermath

On 29 March 2017, the UK served its notice of withdrawal on the European Council under Article 50 of the Treaty on European Union. Article 50 states that:

Any Member State may decide to withdraw from the Union in accordance with its own constitutional requirements.

It is highly probable that the majority of voters had not given much thought to the manner of the UK leaving the EU. It is likely that many thought of the process as being similar to leaving the local golf club; you resign, pay no more fees but receive no more services or privileges. Even those that had read the second clause of Article 50 probably still assumed that the process would be remarkably simple:

A Member State which decides to withdraw shall notify the European Council. In the light of the guidelines provided by the European Council, the Union shall negotiate and conclude an agreement with that state, setting out the arrangements for its withdrawal, taking account for its future relationship with the Union. That agreement shall be negotiated in accordance with Article 2183 of the Treaty on the Functioning of the European Union. It shall be concluded on behalf of the Union by the Council of the European Union, acting by qualified majority, after obtaining the consent of the European Parliament.

This second clause dispels the golf club myth. Any departure from the European Union must be agreed by the European Council and by the European Parliament. This agreed withdrawal is what some refer to as soft Brexit – a civilised and orderly withdrawal with future trade agreements and other future benefits defined. A soft Brexit may involve retaining membership of the EU's single market for goods and services, and possibly some free movement of people. The Chequers Plan, named after the official country residence of the Prime Minister, envisages some aspects of a soft Brexit.

The third clause of Article 50 states that the European treaties shall cease to apply to the withdrawing state from the date of entry into force of the withdrawal agreement. An option that the majority of voters would probably agree with. However, this third clause goes on to say: *or, failing that, two years after the notification referred to in paragraph 2...*, in other words, two years from the day that the UK invoked Article 50 or 29 March 2019 – at 23:00. This means leaving the EU without any agreement or consent by the European Parliament unless an extension period is agreed. This is the form of Brexit known as hard Brexit. The major implications of leaving without an agreement in place under a hard Brexit is that all the EU treaties shall cease to apply. Any trade with the EU and its Member States would have to follow World Trade Organisation rules on tariffs. A hard Brexit would exclude free movement of people between the UK and EU, no freedom to establish and provide services, and no free movement of capital.

Since the referendum, there has been a further lively debate on Brexit in the UK (and elsewhere). Most people want to achieve a negotiated settlement. However, others, especially 'Brexiteers', just want the UK to leave the EU, with a hard Brexit if necessary. The prevailing view for them is that even if we end up with WTO terms and tariffs with the EU, then the UK can negotiate advantageous trade deals with other countries.

At the time of writing in autumn 2018, there is still no agreement between the UK and the other EU Member States and the European Commission, and the complexities have become much more apparent since the vote to leave. This is not surprising since only three countries have left the EU previously (French Algeria on gaining independence in 1962, Greenland in 1985 following a referendum and Saint Barthélemy in 2012; the latter two are now Overseas Countries and Territories of the EU) and so there is little or no past experience on which to draw. Many issues have been resolved but two major ones remain outstanding; the magnitude of the 'divorce bill' and borders on the island of Ireland. The 'divorce' bill is the amount the UK must pay to honour its commitments to EU bodies and other initiatives. These include, but are not limited to, the European Development Fund and the European Investment Bank. The size of the payment is undefined but estimates vary between £36 and £50 billion, while Theresa May has suggested £27 billion. The 'Irish border issue', a common but misleading term, has thus far proven to be insurmountable. The current border is in fact a border between the UK and the Republic of Ireland. As both are EU countries, there is very little border to be concerned about. Once the UK leaves the EU, this border effectively becomes a border between the EU (republic of Ireland) and a third country (the UK). The border issue is problematic because at the moment it enjoys frictionless crossings like any other border between EU countries, but with additional benefits conferred by the Good Friday Agreement of 1998, a treaty which brought peace to Northern Ireland.[3] Once the UK has left the EU, there are fears that a 'hard' border might return along with customs infrastructure and crossings posts. George Mitchell, one of the architects of the Good Friday Agreement, has expressed concern that a hard border between the UK and the Republic of Ireland could jeopardise the Good Friday Agreement and lead to a return to 'the troubles.'[4] This latter issue awaits resolution. Both the UK and the EU want to avoid a 'hard border' in Ireland but neither can agree how to achieve this. One solution proposed is the so-called backstop, a proposed solution that has proved to be controversial. The backstop may be viewed as a safety net which will apply if no agreement on the border is reached in order to keep it 'frictionless'. The backstop proposed by the EU is that Northern Ireland remains in the EU customs union, large parts of the single market and EU VAT (value added tax) systems. The UK is vehemently opposed to this. This would be almost equivalent to Northern Ireland remaining in the EU while the rest of the UK leaves, and the suggestion is unacceptable to many politicians in the UK, including the Prime Minister. As an alternative, the Prime Minister has suggested a backstop where the whole UK remains aligned with the EU customs union for a limited time after the transition period in 2020. The Republic of Ireland Taoiseach, Leo Varadkar is opposed to this because it gives the UK a unilateral position in deciding when this backstop ends. Ultimately, this border issue could decide the issue on whether the UK has a hard or soft (or something in between) Brexit.

Consequences for Regulation of Medicines

One of the immediate consequences of Brexit is that the European Medicines Agency (EMA) will leave the UK and relocate to Amsterdam in the Netherlands. There, it will resume its work by 30 March 2019. In addition, the UK will no longer be able to act as a rapporteur or co-rapporteur for applications considered under the centralised procedure (human or veterinary) or for applications for maximum residue limits (MRLs). For human and veterinary medicinal products already authorised through the centralised procedure, a redistribution of portfolios to the remaining 27 EU Member States and to Iceland and Norway has already occurred. The EMA has published a document establishing cut-off dates for the UK accepting rapporteur and co-rapporteur appointments for regulatory procedures overseen by the Agency.5 An EMA working group on operational preparedness for veterinary medicines has been established, along with an EMA working group on committees' operational preparedness for human medicines. Following Brexit, the UK will no longer take part in meetings overseen by the EMA such as those of the Committee for Medicinal Products for Human Use (CHMP) and the Committee for Medicinal Products for Veterinary Use (CVMP) and their subcommittees and working parties, as well as the EMA Management Board.

Such is the concern over the UK exiting the EU with a hard Brexit, the Department for Exiting the European Union has published a series of over one hundred Guidance notes covering a range of topics including driving and transport, importing and exporting, money and tax, regulating energy, satellites and space, travelling between the UK and the EU and workplace rights. These notes include three concerning veterinary medicines and six regarding human medicines and medical equipment.

There is complex and comprehensive legislation covering the regulations of chemicals in the EU. This includes industrial commodity chemicals, pesticides, biocides, animal feed additives, cosmetics, food additives and air quality in addition to veterinary and human medicines.[6] For human and veterinary medicines, regulation is through four main procedures, the national procedure for medicines only

intended for authorisation in a single EU Member State, the decentralised and mutual recognition procedure for medicines intended for authorisation in more than one EU Member State, and the centralised procedure through the EMA for medicines intended for authorisation throughout the EU.[7,8] MRLs are agreed at EU level through a procedure similar to the centralised procedure. In the mutual recognition and decentralised procedures, Lichtenstein, Norway and Iceland may also be included and through the centralised procedure, Lichtenstein, Norway and Iceland are included. The outcome, if positive, for the decentralised and mutual recognition procedures are a series of national authorisations achieved by a harmonised approach while the outcome of the centralised procedure is an EU-wide authorisation. Similarly, MRLs for ingredients in veterinary medicinal products intended for use in food-producing animals are subject to an EU-wide authorisation. Pharmacovigilance for human and veterinary medicinal products authorised through the centralised procedure is co-ordinated through the EMA, while pharmacovigilance for products authorised under the decentralised and mutual recognition (and national) procedures is co-ordinated through the Member States.[9, 10] After a hard Brexit, the UK will no longer participate in these procedures. So, what will happen to the regulation of veterinary medicines? This is explained in the three Technical notices mentioned earlier, all of which are available on the website of the Veterinary Medicines Directorate (VMD), the UK regulator for veterinary medicines (https://www.gov.uk/government/organisations/veterinary-medicines-directorate). All three notices contain the proviso 'in the unlikely event there is no agreement between the UK and the EU regarding future arrangements…'.

One of the documents is entitled 'Registration of veterinary medicines if there's no Brexit deal.' It covers five main topics:

- Batch testing of veterinary medicines
- Qualified person (QP) batch certification and release of veterinary medicines
- Wholesale dealers authorisations
- Manufacturing authorisation requirements for imported medicinal products from the EU/EEA
- Centralised veterinary medicine authorisations

Under EU legislation, batch testing by manufacturers that hold a UK manufacturing authorisation may be conducted anywhere in the EU or EEA, or in other countries where the EU has made arrangements. After March 2019 then, mutual recognition of batch testing of veterinary medicines between the UK and EU/EEA would be halted, as would the mutual recognition of batch testing between the UK and third countries where the EU has made arrangements.

To overcome these problems, the UK would, 'for a limited time', continue to accept batch testing of veterinary medicines carried out in EU/EEA or in countries recognised by the EU. The UK would also accept batch certification of veterinary medicinal products by a QP based in the UK or the EU/EEA. Any veterinary medicine imported into the UK from a third country would continue to need batch testing in the UK and certification and release from a QP based in the UK or EU/EEA, except where the third country was one of those recognised by the EU/EEA. For companies where the batch release site is located in the UK, then the company concerned will need to establish a location within the EU or EEA. For veterinary medicinal products authorised through the centralised procedure, the VMD will convert these to UK national marketing authorisations unless the authorisation holder prefers not to have these converted. In these circumstances, the product will no longer be available on the UK market. As all products authorised through the mutual recognition and decentralised procedures are, if the UK was included, already national authorisations, then no major changes are envisaged.

A further document entitled 'Regulation of veterinary medicines if there's no Brexit deal' envisages what will happen after March 2019. It notes that the UK is currently part of the EU regulatory framework and of the EMA. This will no longer be the case after a no-deal, hard Brexit. As a result, the UK would need to make its own regulatory arrangements so that veterinary medicines could be authorised. In addition, sharing of systems (e.g. IT) and the exchange of information and data would cease. The UK would have to change its own veterinary medicines regulations to allow veterinary medicines to be authorised on its own territory. This would then mean that the applicant would need to be established in the UK. At the present time, the applicant may be established anywhere in the EU/EEA. The VMD notes that this would enable the UK to accept the QP for release and the QP responsible for pharmacovigilance (QPPV) to be based outside of the UK.

A hard Brexit would have serious consequences for the authorisation of generic products. At the moment, the reference product (the originator product) may be authorised anywhere in the EU/EEA for the UK to consider a generic application. After a hard Brexit, where the UK no longer has access to data considered by other Member State authorities, this will no longer be possible. To apply for a generic after Brexit, the reference products must be authorised in the UK. However, existing authorisations for generic products based on EU-registered reference products will be unaffected unless changes were required in the future. In these circumstances, original data would have to be submitted to the VMD.

Existing EU MRLs would become law in the UK through the EU Withdrawal Act. The VMD rightly notes that this ensures that the UK can continue to trade in food of animal origin with the EU and with countries that recognise EU MRLs without the construction of further barriers to trade. For new active ingredients intended for use in food-producing animals, the UK will establish its own MRL values and safety and residues data will need to submitted to the VMD. This will permit the UK to set MRL values different to those set by the EU but the guidance notes that there will be the powers to set MRLs based on data from a range of sources including 'other MRL setting bodies.' This would at least minimise any divergencies with the EU's MRL values, thus preventing further barriers to trade. The VMD points out that UK exporters of animal produce will need to comply with EU MRL values if the EU is the export destination.

The third document in the series is entitled 'Accessing animal medicine IT systems if there's no Brexit deal.' There are numerous EU IT systems for both human and veterinary medicines which are available to regulatory authorities and/or applicants or marketing authorisation holders. For veterinary medicines, the most important are:

The Common European Submission Portal (CESP) – This is a delivery system that allows applicants for marketing authorisations and variations destined for European regulatory authorities to use a single portal for submissions. It is used for veterinary and human medicines applications. Currently, the system is not used for centralised procedures or MRL applications as the EMA is not involved in the system. The EMA has its dedicated systems for human and veterinary medicine applications and for MRLs.

Following Brexit, the UK authorities will not have access to CESP and documents entered into CESP will not therefore be delivered to the VMD. However, applicants based in the UK will still have access to CESP. The VMD intends to develop systems for the submission of UK– only applications. It intends to ensure that these are available for March 2019.

The Gateway and the Webtrader – Both these systems exist so that pharmacovigilance information can be processed through Eudravigilance Veterinary (EVVet). EVVet is a data-processing network and database management system for pharmacovigilance operated on behalf of the EU medicines regulatory authorities by the EMA. Although companies based in the UK will still be able to use this after Brexit to submit pharmacovigilance data on any European marketing authorisations which they hold, the VMD will no longer have access. Again, the UK is developing systems to deal with pharmacovigilance data for UK-only marketing authorisations.

EudraLink: EudraLink is a secure messaging system which allows message interchange between companies and European medicines regulators. The only requirement for a workstation is the availability of a web browser and an e-mail system. The VMD will cease being a part of the network, although there is no reason why it may not have 'personal' access of the type available to companies and consultants.

The VMD has promised to minimise impact wherever possible. It will continue to accept EU format and standard applications for data submission but more importantly, it has also promised to have its own systems in place by the time the UK exits the EU.

Conclusions

The United Kingdom is currently working with the EU and the European Commission in order to achieve a Brexit deal which is satisfactory to both sides and which ultimately leads to a negotiated settlement. It would appear that many issues have been resolved and some, like the 'divorce bill' are subject to further negotiation. However, the border between the EU and the UK as a third country on the island of Ireland is very problematic and this may decide the nature of the Brexit deal or the absence of a Brexit deal. In the event that there is no Brexit deal, the UK's VMD is putting into place measures which will allow the registration of medicines to continue in the UK.

The difficulties associated with Brexit were highlighted on the 15 November 2018 following the publication the previous day of a draft document setting out proposals for the UK's departure from the EU[11]. On the 15 November, four ministers, with two from the Department for Exiting the European Union, resigned from the government over the document's content. One of these ministers was the Secretary of State for the Department, Dominic Raab. None of this augurs well for a successful conclusion to the negotiations but, if there is a Brexit deal, new issues are raised. The UK will still not be a member of the EU. So, what will its relationships with EU member states and the EMA be then? Will some of the measures proposed for no-Brexit still have to be introduced for a fully negotiated Brexit and, if so, which ones? Will other measures be needed? Perhaps these are topics for a future paper in this journal.

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