Brexit and Drugs

This is a short "guide" to the issues and uncertainties arising for the UK around Brexit inasmuch as they affect the use and regulation of pharmaceutical drugs. I apologise to those who are expecting a talk on decriminalisation of illicit substances as part of the Brexit negotiations - or hoped to enjoy a crafty but legal joint on 1 April 2019. Interesting is that subject may be, it will have to wait for another day.

This talk is – like Gaul - divided into three parts, namely:

- What is the position at the moment
- How will the position change if the UK becomes a "third country" for the purposes of the European Medicines Agency ("the EMA"); and
- What possible compromise may be agreed to keep aspects of the EMA regulatory framework operating within the UK post Brexit.

Part 1 : How do things operate at the moment?

As Dr Peter Feldschrieber noted in his introduction to the Law and Regulation of Medicines[1]:

> "The control of medicinal products by the state has a long and somewhat dishonourable history"

It dates back to the Apothecary, Wares, Drugs and Stuffs Act 1450 which provided for searches of apothecaries (that is an early name for those who sold medicines) as follows:

[1] OUP: 2008

> "If the search showed that drugs that were defective, corrupted did not meet not convenient to be ministered in any medicines for the health of man's body, the searchers with a call for the wardens of the Apothecaries and defective wares to be burnt or otherwise destroyed"

Thus, dealing in defective medicines was a hazardous business in 1450. There followed a long history of regulation of medicinal products, which eventually recognised that a medical regime needed to focus on two objectives.

- The first was to prevent medicines being marketed which were dangerous to health, particularly if they had unwelcome side-effects, notably arising from the thalidomide disaster. This was the original sole focus of the regulation of "patent medicines" which claimed to cure all manner of ailments.

- The second objective emerged in the 20th century, namely attempts by government agencies to assess the efficacy of medicinal products as **a** treatment for specific medical conditions. The question as to precisely how it could be shown that a medicine was clinically effective was subject to considerable scientific debate and remains contentious, particularly where the placebo effect is scientifically demonstrated. The system of clinical trials now underpins the need to demonstrate clinical effectiveness before a marketing authorisation is granted for a medicine although, even these, can be manipulated or only selectively reported. For further details see Dr Ben Goldacre's excellent writings about the shortcomings of the process for testing whether medical treatment is or is not clinically effective.

Today the European Medicines Agency (EMA) primarily discharges these functions across the EU and EEA countries. It is an agency of the European Union (EU), which is located in London but is due to move to Amsterdam as a result of Brexit. It began operating in 1995.

The Agency is responsible for the scientific evaluation, supervision and safety monitoring of medicines in the EU.

There are three procedures by which a medicine intended for human use can be granted a marketing authorisation within the EU. First, there is the centralised procedure. The centralised procedure allows the marketing of a medicine on the basis of a single EU-wide assessment and marketing authorisation which is valid throughout the EU. Pharmaceutical companies submit a single authorisation application to EMA. The EMA's Committee for Medicinal Products for Human Use (CHMP) then carries out a scientific assessment of the application and gives a recommendation to the European Commission on whether or not to grant a marketing authorisation. Once granted by the European Commission, the centralised marketing authorisation is valid in all EU Member States. The use of the centrally authorised procedure is compulsory for most innovative medicines, including medicines for rare diseases. The majority of medicines authorised in the EU do not fall within the scope of the centralised procedure but are authorised by national competent authorities (NCAs) in the Member States.

The UK NCA is the Medicines and Healthcare Regulatory Authority, known by its initials as the MHRA.

When a company wants to authorise a medicine in several Member States, it can use one of the following procedures:

- the decentralised procedure where companies can apply for the simultaneous authorisation of a medicine in more than one EU Member State if it has not yet been authorised in any EU country and does not fall within the scope of the centralised procedure;

- the mutual-recognition procedure where companies that have a medicine authorised in one EU Member States can apply for this authorisation to be

recognised in other EU countries. This process allows Member States to rely on each other's scientific assessments.

Rules and requirements applicable to pharmaceuticals in the EU are the same, irrespective of the authorisation route for a medicine.

It must be stressed that this process is solely concerned with the marketing of medicines within the EU, and a drug "licence" is a marketing authorisation, not a licence which permits doctors to use the medicine for a particular purpose.

The use of medicines within a state healthcare system is a matter of national competence. Article 168 of the Treaty for the Functioning of the European Union specifically excludes EU competence in the management of member state healthcare systems. Nonetheless, a member state healthcare system cannot legislate to permit the general importation and purchase of medicinal drugs which do not have a marketing authorisation which are cheaper and have similar features to drugs with a marketing authorisation: see *EU Commission v Poland*.

The extent to which the NHS is free to adopt policies to promote off label use of pharmaceutical products will be examined by the High Court in a case concerning the use of Avastin for age-related macular degeneration this July. I, along with David Bundell of the chambers, act for the NHS bodies in this case which has its own very particular features, but in essence will consider whether it is lawful to use a drug of label – at 1/20th of the cost - in preference to drugs which have a marketing authorisation for the particular condition.

How will things change with Brexit?

The present EU scheme for regulation of medicines applies to the 28 present EU member states plus Iceland, Lichtenstein and Norway (i.e. the EEA countries). There is also an

associate membership agreement between the EMA and Switzerland which provides for the EU medicines regime to operate within Switzerland.

The EMA has already indicated intention to remove central operations from London to Amsterdam as a result of Brexit.

When addressing the UK Parliament Health Select Committee in January 2017, the Secretary of State, Jeremy Hunt, said:

> "I do not expect us to remain within the European Medicines Agency, but I am very hopeful that we will continue to work closely with the EMA"

Interestingly, the Secretary of State for Exiting the EU subsequently said that Mr Hunt did not say that the UK would leave the EMA and had been misquoted and misinterpreted. The problem with that suggestion is that Mr Hunt's remarks were recorded and on the record. The Academy of Medical Royal Colleges has expressed concern about the practical effects of leaving the EMA. It said:

> "If not part of the EMA we would be unable to participate in the European wide approval system the new medicines and the revisions to already approved products, to participate in the Orphan Drug Designation and the Small to Medium Sized Enterprise schemes that the EMA operate or participate in the specific centralised approval process for paediatric drugs and the process that supports new medicines development for children. We would lose access to the EU wide Pharmacovigilance networks and the EU Clinical Trials Database"

On 11 April 2018 the EMA published guidance to assist marketing authorisation holders to prepare for Brexit. This confirmed that, as a result of Brexit "The United Kingdom will then become a "third country" for the purposes of the EMA regulatory scheme. It said:

> "As a consequence, the MHRA … Will no longer be able to engage in centralised regulatory procedures .."

In further guidance, the EMA has confirmed that, in preparation for the UK's withdrawal from the EU, a marketing authorisation holder currently established in the UK will need to be replaced with a marketing authorisation holder established in one of the remaining countries of the EEA. This change in MAH requires an application transfer of marketing authorisation from the current UK- based MAH to a different legal entity established in the EEA.

It follows that the MHRA will transfer from being a National Competent Authority within the scope of the EMA regulatory structure to be a national medicines authorisation agency for a state which is wholly outside the EU.

A combination of the positions published by the EMA and the European Union (Withdrawal) Bill suggests that the withdrawal of the UK from the EU in March 2019 will have four primary consequences for the operation of the pharmaceutical market in the UK:

a) Post Brexit, new decisions by the MHRA will have effect in the UK only but will have no effect within the other 27 members of the EU and EEA countries. Thus the MHRA process will be of no practical benefit to any UK-based pharmaceutical company that wishes to market its pharmaceutical products across the EU;

b) If section 3(1) of the European Union (Withdrawal) Bill becomes law, both past and future marketing authorisations granted by the EMA and by National Competent Authorities in other EU and EEA countries will operate as effective marketing authorisations to permit the marketing of EU approved medicines in the UK. Thus the EMA and National Competent Authorities in each of the EU and EEA member states will be able to continue to issue marketing authorisations

which will permit new medicines to be marketed in the UK, even though the UK will not be part of the EMA;

c) Both past and future decisions of the European Court of Justice about the meaning and effect of the EU regulatory medicines regime will cease to be binding on UK courts but will only be matters to which the court has a duty to have regard when making decisions about how the regime operates in the UK: see clause 7 of the Bill.

In practical terms, this will reduce the importance of the MHRA because authorisations granted by that body will cease to have any relevance to the rest of the EU and EEA. It will also mean that future changes to the European drug regulation regime will continue to have effect within the EU but will not have effect within the UK. In practical terms, it is difficult to see how this will work itself out in circumstances where there are Post Brexit changes to the European drug regulation regime (which will not apply to the UK) and decisions are made to grant marketing authorisations under that amended regime.

There should be no immediate direct effect on clinical trials because it is theoretically possible to operate clinical trials within the European drug regulation regime. However a new Clinical Trials Regulation is due to come into force in 2019 which will make it increasingly difficult for clinical trials to be conducted outside the EU as part of any EU based application for a marketing authorisation. By way of example, the Regulation provides that all clinical trials need to be approved in advance by an ethics committee of a Member State. Post-Brexit, the UK will not be a member state and therefore approval by a UK-based ethics committee will not comply with article 4 of this Regulation.

It thus seems likely that, unless something can be negotiated to ameliorate position, there will be a substantial reduction in the number of clinical trials which are conducted in UK-based hospitals. This potential reduction has three serious consequences:

a) First, NHS patients will not have access to new and emerging drug therapies by taking part in clinical trials. My own brother is being treated for lung cancer at present and is part of a clinical trial which has resulted in very substantial improvements to his health. It is no exaggeration to say that he is alive and reasonably well today whereas, if you did not have the opportunity to take part in the trial and had not responded so well, it is hugely probable that he would have died. Much of this research is funded by pharmaceutical companies and charities, all of whom are aiming to secure marketing authorisations for the medicinal intervention question. A large number of these trials are multi-centred, with corporation between doctors working in different countries. However, very little of this research is funded by the NHS. However, it seems inevitable that there will be a substantial diminution in the number of UK-based the centres where research takes place in a future. That means that there will be fewer opportunities available to NHS patients in the future unless the clinical trial issues are addressed;

b) Secondly, taking part in ground-breaking research is a key part of the role of leading consultants in our teaching hospitals. Our best medical minds combine treating patients and undertaking research. These individuals are in huge demand across the world and many are either non-UK nationals already have very strong links to other countries as a result of international nature of medical careers. They are in a strong position to take their expertise abroad. It seems inevitable there will be a medical brain drain if they are unable to secure funding to continue research;

c) The UK pharmaceutical industry is one of the great success stories of the UK economy. Pharmaceutical companies are unlikely to move abroad overnight, but the UK will become a considerably less attractive place to operate.

What can be salvaged as part of the negotiations?

In April 2017 the Health Select Committee produced a report on Brexit and health and social care. This raised serious issues about the future relationship between the UK the EMA. The government produced a detailed response which addressed all of the issues raised by the Committee apart from the future relationship between the UK and the EMA. There was no answer to the stinging criticism made by the committee that the government had no plan to explain how it proposed to construct a medical regulation regime outside the EU which served the interests of the UK.

Speaking on 2 March 2018 the Prime Minister said:

> "We will also want to explore with the EU, the terms on which the UK could remain part of EU agencies such as those that are critical for the chemicals, medicines and aerospace industries: the European Medicines Agency, the European Chemicals Agency, and the European Aviation Safety Agency.
>
> We would, of course, accept that this would mean abiding by the rules of those agencies and making an appropriate financial contribution.
>
> I want to explain what I believe the benefits of this approach could be, both for us and the EU.
>
> First, associate membership of these agencies is the only way to meet our objective of ensuring that these products only need to undergo one series of approvals, in one country.
>
> Second, these agencies have a critical role in setting and enforcing relevant rules. And if we were able to negotiate associate membership we would be able to ensure that we could continue to provide our technical expertise.
>
> Third, associate membership could permit UK firms to resolve certain challenges related to the agencies through UK courts rather than the ECJ"

It is entirely possible that something along the above lines could be negotiated, notwithstanding the frosty reception that the proposals initially received from the EU. However, the politics on both sides means that exactly how any form of associate membership would operate in practice would be far from straightforward.

There will be strong pressures in the EU to avoid the UK having the economic and social benefit of EU rules in areas where it sees they have advantages but to avoid other EU rules where they are perceived to have disadvantages for the UK. It is difficult to underestimate the importance for the rest of the EU of preventing any settlement with the UK which could be described as "cherry picking". Thus, it will probably not be open to the UK to produce a shopping list of EU institutions that it wishes to remain part of vast, same time, removing itself from any need to comply with the remainder of the rules of the single market. Having said that, the UK domestic pharmaceutical industry is sufficiently strong and well-connected throughout Europe and the NHS is so totemic that a special arrangement for medicines may be easier to sell than special arrangements in other areas.

Nonetheless it seems inevitable that any form of associate membership will need to include an acceptance by the UK of the ultimate primacy of the European Court of Justice in interpreting the meaning of the regulatory regime relating to medicinal products. The EU is never going to agree to an "associate member" who reserves the right to decide for itself how the rules of the club operate.

So, this proposal would involve crossing a "red line" for the UK government.

The devil will be the detail for any halfway house involving associate membership of the EMA. I strongly suspect that the EU will drive a hard bargain but, ultimately, we will remain subject to all of the rigours of the present regime, and only lose our ability to influence future changes to it.

However, that may prove to be too optimistic.

12th June 2018.

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