



BREXIT IMPLICATIONS FOR THE UK PHARMACEUTICAL INDUSTRY

by Pete Gough

The only thing that is certain following the UK's momentous decision to leave the European Union (EU), so called Brexit, is that the pharmaceutical industry, as all others, is facing at least two, and probably many more, years of unprecedented uncertainty.

One theoretical possibility is that the UK will seek to join Norway, Lichtenstein and Iceland in the European Economic Area (EEA). If this were to happen, then in practical terms for medicinal products comparatively little would need to change. However, politically, it would appear to be very unlikely that the UK will seek to join the EEA.

If the UK does not elect to join the EEA, it will become a third country as far as the EU is concerned and this will lead to much more profound changes.

In late August 2017 the UK government published its Brexit position paper, Continuity in the availability of goods for the EU and the UK. In this paper, the government says that any marketing authorizations or other approvals issued before Brexit "should continue to be recognised as valid by both markets after the UK's withdrawal." It adds that there should be no requirement to re-inspect manufacturing facilities approved before the UK's departure from the EU.

It is the UK government's desire to maintain the "deeply integrated trade and economic relationship" between the UK and the EU after Brexit, and to provide legal certainty and avoid disruption for business and consumers with respect to the continued availability of goods in the EU and the UK. The position paper states that "In doing this, it makes sense to recognise our common regulatory systems and the UK's ambition for cooperation in the future."

According to the paper, a "key element" of delivering a "smooth, orderly exit" from the EU for business and consumers is ensuring that products can be lawfully marketed in the UK and the EU. This includes goods that are placed on the market before the date of withdrawal but cross the UK/EU border after exit.



"The UK's position is that these should be discussed and resolved in a way that supports the move to a future relationship."

Any further compliance activity required after Brexit as a result of the prior compliance activity should be conducted as originally intended. The paper states that "This would avoid business and authorities in both the EU and the UK needing to undertake significant duplicative compliance activity after exit, for example to re-inspect approved manufacturing plants or collect and submit data again."

One example is the role of a Qualified Person in testing and batch release of medicines. Here, the government says it "wants to avoid unnecessary disruptive transfer of activities between the EU and the UK, and these ongoing activities being duplicated for both markets, particularly where the UK's aim is for this activity to be recognised as part of a future relationship."

The UK's proposals may well be perceived by the EU as yet another example of the UK wanting to "have its cake and eat it too." Already the Commission is seeing that other EU Member States are being more assertive in pushing their national agendas on a range of issues. This is likely to mean that it will not want to be too accommodating of the UK in the future trading relationship.



On 21 September, the UK Parliament's Commons Select Health Committee announced the launch of an inquiry into the regulatory arrangements needed to guarantee safe and effective supply of medicines, medical devices and products post-Brexit. The Health Committee asked to receive feedback from companies and industry associations on the following questions, and public hearings are expected to be held in December 2017:

- > What are the key considerations that arise for companies, health care 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?
- > 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?
- > 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?
- > How will withdrawal from the European Union affect the UK's ability to influence international standards in life sciences?
- > What arrangements are needed to ensure the safe, effective and timely supply of medical radioisotopes over the short, medium and long term?
- > What are the implications for medical research and development, including timely patient access to new medicines, technologies and other relevant medical innovations developed within or outside the UK? How can any adverse consequences be avoided or mitigated and any potential opportunities be enhanced?

EUROPEAN MEDICINES AGENCY (EMA) RELOCATION

The European Medicines Agency (EMA) has to move its headquarters from London to another EU Member State. The location of the new host city, Amsterdam, was announced on 20 November 2017. After a series of votes eliminated the other contending cities, the vote was tied 13 for Amsterdam and 13 for Milan (Slovakia abstained from voting after its candidate city, Bratislava, was eliminated on the first vote), so the choice was made by drawing a name out of a hat.

The choice of Amsterdam has generally been well received by industry and by the EMA itself. The EMA's executive director Guido Rasi remarked that it "ticks many of our boxes" and said that a joint governance structure would be set up to oversee the relocation project. Amsterdam was one of the cities that an internal poll within the EMA indicated had the best chance of retaining a significant proportion of its existing staff and hence minimise the disruption to work as result of the move.

On 1 August 2017 the EMA published a continuity plan to ensure that it can handle the inevitable disruption caused by the relocation. This plan prioritised activities into three categories, where category 1 was the highest priority and category 3 the lowest. The EMA also announced that it would be scaling back the following category 3 activities:

- > Development of the European Medicines Web Portal
- > EMA's contribution to the e-submission project
- > Participation in the benchmarking of medicines regulatory authorities
- > The number of audits and some corporate governance and support activities

The plan said that category 1 and 2 activities would be maintained for now and that the EMA will update the plan as needed. It warned that "Unexpected higher, faster or more permanent loss of staff as a consequence of the Agency's relocation may lead to a situation in which EMA's operations can no longer be maintained."



In September 2017 EFPIA, the trade association for the research-based pharmaceutical industry, published a review that it had commissioned to assess the likely impacts of the relocation of the EMA, which has to occur at the same time as all of the other regulatory activities necessary as a result of Brexit. This review concluded that the most serious impact would be on the EMA's ability to assess new marketing authorisation applications and variations to existing application.



The move of the EMA from London will have resource implications for both the EMA and the UK's Medicines & Healthcare products Regulatory Agency (MHRA). The MHRA has provided the EMA with up to 40 percent of its scientific expertise and has conducted about 25 percent of its overseas inspections. The MHRA has said that it can envisage two possible futures post-Brexit: continue working in partnership with the EMA or operate as a stand-alone agency.

If the MHRA were no longer able to contribute to the work of the EMA, this would severely impact both agencies. The EMA would have to use expertise from other EU Member States' agencies, which would mean recruiting additional staff. The MHRA would lose a significant proportion of its income; in 2016/17 MHRA received £14.5M (8.6 percent of its total income), from work for the EMA.

BREXIT IMPLICATIONS

In late May 2017 the EMA and European Commission published guidance to help pharmaceutical companies responsible for both human and veterinary medicines prepare for Brexit. The question-and-answer document was the first in a series of guidance documents.

The potential changes that would be required with the UK leaving the EU and becoming a third country are:

PHARMACEUTICAL LEGISLATION

Until recently most EU pharmaceutical legislation has been issued as directives, which means that these directives have already been transposed into UK legislation; mostly in The Human Medicines Regulation 2012 (Statutory Instrument 2012-1916). However, this statutory instrument (SI) will almost certainly have to be revised as it has been issued under the authority of the European Communities Act 1972, which will have to be repealed, and contains numerous references to EU directives. The UK government plans to introduce a bill to repeal the European Communities Act 1972, which will simply transpose the existing provisions unchanged, at least initially.

So what will UK pharmaceutical legislation look like moving forward outside of the EU? It all depends on the outcome of the negotiations between the UK and the EU. The most logical outcome for medicinal products would be for the UK to adopt the Swiss model; i.e. the UK would adopt EU pharmaceutical legislation into UK law so that UK medicines law shadows EU medicines legislation while it remains outside of both the EU and the European Economic Area (EEA). This would require the least re-writing of the existing UK legislation and could be applied to future EU changes whether they are issued as directives or regulations.

GMP AND OTHER REGULATORY GUIDANCE

The UK MHRA has always had significant input into the development of GMP and other medicinal product guidance and the EU GMP guide has been heavily influenced by the UK inspectors. However, the European Commission has published plans and draft text that fragment EU GMPs, with separate GMPs for marketed products, IMPs and ATMPs. This has been opposed by all EU inspectors, but the Commission appears to be pressing ahead regardless. It is possible



that the UK could choose not to follow this breakup of GMP, especially if the Pharmaceutical Inspection Co-operation Scheme (PIC/S) chooses to also depart from the EU model.

The MHRA will undoubtedly want to continue to influence via organisations such as PIC/S, where it recently had chairmanship, and probably the International Council for Harmonisation (ICH). It is expected that the MHRA would become members of the recently re-organised ICH so it can continue to participate in this highly influential forum and continue to provide its valuable contributions to the evolution of GMP and other guidance.

MRAS, REGULATORY INSPECTIONS AND IMPORTS

If a mutual recognition agreement (MRA) or an agreement on conformity assessment and acceptance (ACAA) is agreed prior to the UK exiting the EU, not much will change between the UK and the EU. Without MRAs or ACAAs, UK companies would be subject to inspections by EU authorities and the MHRA would be required to inspect in EU Member States, which it does not have sufficient inspection resources to do at present.

The UK will need to agree its own MRAs with the countries who currently have MRAs with the EU. This should be possible but will add to the MHRA's work in the short term conducting any assessments needed and additional inspections if there is a lag between the UK leaving the EU and the signing of UK MRAs.

If MRAs are not place when the UK leaves the EU, product exported from the UK to the EU would need to be re-tested on importation to the EU. The UK could choose if it also wishes to test product coming into the UK from the EU. On a practical level this could mean that hundreds of analytical methods would need to be transferred.

The MHRA could lose its access to the EudraGMDP database and, in that case, its inspection outcomes would no longer be entered.

QUALIFIED PERSONS (QPS)

The role of the QP is already enshrined in UK law by SI 2012-1916, so providing that the UK agrees to mirror EU legislation, as described above, there should be no change in terms of the requirements to become a QP in the UK or in a QP's role in the certification of batches.

Obviously, if the UK is no longer in the EU, UK QPs will no longer be able to accept certification of products by EU QPs and vice versa. This is likely to increase the workload for QPs in the UK and in the EU for product coming from the UK.

QPs who became eligible in another EU Member State and are named on UK manufacturing or importation authorisations (MIAs) would be an issue. Hopefully, some sort of grandfather clause might be negotiable but it is possible that they may no longer be eligible. The reverse is also true with UK-origin QPs no longer being able to be named on MIAs in the remaining 27 EU States.

MARKETING AUTHORISATIONS

A lot is unknown but it is likely that the MHRA will have to mutually recognize centralized (EU) authorisations and introduce a process to issue a national marketing authorisation (MA), much like Norway and Iceland do at present.

In May 2017 the European Commission and EMA jointly issued a document, Notice to marketing authorisation holders of centrally authorised medicinal products for human and veterinary use. In this document the Commission reminds companies that from midnight on 30 March 2019 the UK is no longer part of the EU and becomes a third country. The notice continues as follows:

“In this regard, marketing authorisation holders of centrally authorised medicinal products for human and veterinary use are reminded of certain legal repercussions, which need to be considered:

- > EU law requires that marketing authorisation holders are established in the EU (or EEA)
- > Some activities must be performed in the EU (or EEA), related for example to pharmacovigilance, batch release etc



Preparing for the withdrawal is therefore not just a matter for European and national administrations, but also for private parties. Marketing authorisation holders may be required to adapt processes and to consider changes to the terms of the marketing authorisation in order to ensure its continuous validity and exploitation, once the United Kingdom has left the Union.

Marketing authorisation holders will need to act sufficiently in advance to avoid any impact on the continuous supply of medicines for human and veterinary use within the European Union.

In particular, the Commission and the European Medicines Agency expect marketing authorisation holders to prepare and proactively screen authorisations they hold for the need for any changes. The necessary transfer or variation requests will need to be submitted in due time considering the procedural timelines foreseen in the regulatory framework.

The Commission and the European Medicines Agency stand ready to support marketing authorisation holders and will provide a series of Q&As. A dedicated page of the Agency's website, http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/general/general_content_001707.jsp&mid=WC0b01ac0580a809a7, already contains general information pertaining to the outcome of the UK referendum. This page will be updated with further practical information and relevant Q&As from May 2017 and will be subsequently expanded, where necessary."

For decentralised and mutual recognition procedures (MRPs/DCPs), companies will probably begin moving away from the UK quite quickly. For existing MAs linked to an EU procedure, where the UK is the Reference Member State (RMS), in the long term, the role of the RMS will need to migrate to another EU Member State. Transfer from one RMS to another currently requires the initial RMS to prepare an assessment report. The MHRA will be hard-pressed to do this for every MRP/DCP that it leads, so some form of interim process will be required.

Where the UK is a Concerned Member State in an established EU MRP/DCP, pan-EU variations procedures will no longer apply in the UK, leading to a significantly bigger workload for the MHRA; the UK will have to

assess changes for all previously EU-based MAs, with the consequential increase in approval times.

Degrees of regulatory disruption and chaos will be inevitable over the coming months, even if the MHRA introduces some pragmatic processes to migrate licences linked to EU procedures into UK national procedures.

The EMA also subcontracts a large quantity of assessments to the MHRA, which will presumably cease, meaning the EMA response times may also increase for handling applications etc.

CLINICAL TRIALS

This area is in the process of major change with the implementation of the Clinical Trials Regulation No. 536/2014. As this is a regulation, it has not until now required translation into UK law. If the UK chooses to follow the Swiss model, this translation would need to occur when the UK leaves the EU. This regulation is due to be implemented sometime during 2019, around the same time or after the UK formally leaves the EU on 29 March 2019.

API IMPORTS

The UK will need to apply to go on to the Commission's white list of non-EU acceptable active pharmaceutical ingredient (API) exporting countries. If the UK is not added to the list, the MHRA will have to issue written confirmation of GMP compliance for every API exported from the UK into the EU.

PHARMACOVIGILANCE

- > The current process is dependent on its access to several EU databases and centralised systems, e.g. EudraVigilance. Presumably the UK will no longer have access to these post-Brexit, so new centralised reporting requirements started in November 2017. The UK may have to have its own system.

Also UK-based Qualified Persons Responsible for Pharmacovigilance (QPPVs) will probably no longer be eligible in the EU.



PHARMACOPOEIA

The European Pharmacopoeia (PhEur) is prepared, published and distributed by the European Directorate for the Quality of Medicines and Healthcare which is part of the Council of Europe, not the EU. So, providing the UK remains a member of the Council of Europe, which has a total of 47 member countries including Switzerland, not too much should change.

ABOUT THE AUTHOR



A chemist with a master's degree in analytical chemistry, Peter Gough has nearly 40 years' experience of pharmaceutical manufacture, control and quality management, culminating in the role of Senior Quality Consultant in Eli Lilly's Global Quality Systems division. He has broad experience, particularly with quality control laboratories and the manufacture of solid dosage forms and active pharmaceutical ingredients.

SUMMARY

- > If the UK joins the EEA, impact is minimal (but this is highly unlikely).
- > If the UK becomes a third country, changes will likely be profound.
- > Agreeing MRAs and ACAAs, as well as being on the API white list with EU will help reduce some impacts.
- > To avoid issues with the supply of medicines we need sensible, pragmatic decisions from both UK and EU politicians.
- > The UK's position of wanting to continue as if it hadn't left the EU may well not be acceptable to the EU.
- > We will not know the full impact until the UK exit strategy is agreed at highest political level. This is likely to be followed by many more years of work to determine the details.
- > We are entering a period of significant uncertainty. In theory nothing should change until 29 March 2019, but you must start planning for Brexit now!
- > The best advice is to plan for the worst but hope for the best outcome.

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