“BREXIT MEANS BREXIT,” BUT WHAT COULD BREXIT MEAN IN PRACTICE FOR PHARMA?

Emma Beausang, PhD, MRPharmS
Associate Director, Regulatory Affairs
INTRODUCTION
On June 23, 2016, a narrow majority voted in a referendum for the United Kingdom to leave the European Union (52% vs. 48%). With no member country having exited since the EU’s creation in the 1990s, this decision is unprecedented, resulting in uncertainty and speculation as industry attempts to understand its full implications. The UK’s new prime minister, Theresa May, hastily elected after the resignation of David Cameron, came into office proclaiming that “Brexit means Brexit.”

Clearly, continued market uncertainty may impact the health of industry in the UK. However, beyond any general economic considerations, what might the new reality facing the country and the European community be, and, how will the changes impact the pharmaceutical and life sciences industry?

THE STATUS QUO NO MORE
The UK life sciences industry contributes more than £50 billion to the UK economy, and with approximately one-eighth of the world’s most popular prescription medicines being developed in the UK, the industry has a reputation as a world leader in research and innovation. As far as most in the industry are concerned, both UK-based and beyond, the status quo of UK membership in the EU “works.”

The UK pharma industry enjoys many benefits through the country’s existing EU membership. The UK is recognized internationally as a center for research excellence, and, as a EU member, has had access to high levels of EU funding for research, development and innovation. Over the period 2007-2013, the UK received roughly 8 percent of the total research funds available, amounting to €8.8 billion and the fourth highest funding allocation across eligible countries. The current budget for EU research funding over the period 2014-2020 is €120 billion.

In addition, the UK pharma industry has access to a large workforce with all EU nationals possessing the right to work in the UK without needing a work permit or visa. In the first quarter of 2016, approximately 7 percent of the total working population in the UK were expatriate EU nationals.

The European Medicines Agency (EMA), the central regulatory body for the EU, is housed in Canary Wharf in London where almost 900 staff carry out the agency’s business, leveraging scientific expertise from EU national regulatory agencies to evaluate medicinal products, provide scientific advice and monitor the safety of medicines across the EU. The current arrangement for review and approval of medicines’ licensing applications also allows reciprocal benefits regarding the access to medicines in the UK.

Additionally, pharma companies may obtain marketing approval in the UK at the same time as other EU member states while, in turn, the UK population may access all medicines approved either centrally by the EMA or through a
decentralized procedure involving the UK. Likewise, the safety monitoring of medicines in the UK is closely linked to EU-level pharmacovigilance legislation and EMA initiatives. Finally, the review and approval steps required in advance of conducting a clinical trial in the UK are consistent with all other EU member states.

In short, the regulation of medicines in the UK is enmeshed in the EU-level platform to a significant extent. For many, the prospect of unpicking the UK from the current arrangements following an EU exit is daunting to say the least.

THE POST-BREXIT LANDSCAPE

Although some initial opinions suggested the referendum result might be advisory, the UK government has insisted the mandate will be respected and an exit is inevitable. However, the mechanics of a UK exit from the EU are far from clear and the implications of several possible models warrant consideration.

THE NORWAY OPTION

The European Economic Area (EEA), established in 1994, extends the EU’s internal market to include Norway, Iceland and Liechtenstein (non-EU countries). Although EEA countries are not members of the EU, EU legislation relating to the internal market — governing the “four freedoms” of goods, people, services and capital — becomes part of the legislation in EEA countries once they agree to incorporate it. In this way, EEA countries adopt the same rules relating to licensing of medicines and clinical trials as EU member states. National agencies from EEA countries are entitled to standing membership on EMA committees and may act as rapporteur or co-rapporteur in EMA procedures.

A drug approved by the EMA through a centralized procedure is eligible for marketing in EEA countries in parallel with the EU. However, EEA committee members do not have equal voting rights as those committee members from EU member states and cannot act as committee chair or vice-chair. EEA countries can be included in mutual recognition and decentralized procedures in the same way as other EU member states.

Although the Norway option is appealing to the UK pharma industry because it allows pharmaceutical legislation relative to the UK to be largely maintained, one of the central tenets of the EEA — free movement of people — runs contrary to a key factor in the decision taken by so many of the electorate when they voted to leave the EU; therefore, the UK government may find it a tough sell. The Medicines and Healthcare products Regulatory Agency (MHRA) may also find holding a position of less influence in the EMA to be challenging, having been previously accustomed to a leading role.

The Medicines and Healthcare products Regulatory Agency (MHRA) may find holding a position of less influence in the EMA to be challenging...
UK “GOES IT ALONE”

Should imposing some restriction on UK borders be unavoidable, the UK may find itself entirely outside of the EU and any associated constructs. This may be the worst case for the pharmaceutical industry with implications that the regulation of medicines and clinical trials in the UK would be entirely separate from the EU/EEA and that the UK industry would no longer enjoy open access to a large and mobile EU workforce.

It would follow that a national application to MHRA would be required to place a new drug on the UK market. Similarly, although the new EU clinical trials regulation will finally offer a centralized submission route for sponsors planning studies in multiple EU member states, sponsors would need to submit a stand-alone clinical trial application to MHRA post-Brexit.

Furthermore, any sponsor using a UK-based entity as a EU legal representative would need an alternative arrangement. Whether MHRA would continue to recognize GMP certificates issued by other EU national competent authorities or European Directorate for the Quality of Medicines and HealthCare (EDQM) Certificates of Suitability is unknown. If not, the increase in inspection and drug master file review activities combined with the increase in the licensing workload would mean serious resource implications for the MHRA.

Depending on how UK-only regulation evolves, for any company aiming to place a new drug on the market, the requirement to submit to the UK separately from the rest of the EU/EEA risks de-prioritizing the UK from a commercialization strategy. Compromised access to new medicines may therefore be an unwelcome side effect for UK citizens. The UK government may need to explore incentives to preserve UK’s current status as one of the first European countries where new medicines are launched.

Since the referendum, the MHRA has released two statements to reassure the industry and the public that, for the moment, the agency is as active as ever in European procedures. However, a UK exit also has implications for the EMA. It has been widely postulated that continuing to locate the EMA in a country no longer part of the EU is untenable; it is likely the agency will be uprooted from Canary Wharf to the European mainland. Interest in hosting a new agency location from Italy, Sweden and Denmark has been reported so far. In an attempt to dampen speculation, the EMA released a statement in early July to confirm that nothing had been decided and that as far as the agency was concerned it was “operations as usual.”

Should Brexit result in the UK existing outside of the EU and EEA, another impact on the EMA is the withdrawal of MHRA support from the agency’s assessment resource pool, drawn as it is from EU national competent authorities. The MHRA participates significantly in EMA activities, whether it is acting as rapporteur for centralized marketing authorization applications, carrying out pre-approval GMP and GCP inspection activities, leading scientific advice or protocol assistance procedures, or leading...
pharmacovigilance referrals. Aside from centralized procedures, the MHRA also provides significant support to the main alternative licensing route, the decentralized procedure (DCP), acting as reference member state in almost half of all procedures in which the UK is included — meaning a potential increase in workload at other national agencies in a scenario where the UK no longer participates in DCPs.7,8

A SOFT EXIT
One further possible outcome might be that of a hybrid approach whereby the UK may leave the EU but negotiate to become a member of the EEA for a finite time period before eventually establishing itself outside of both. This would minimize day-to-day disruption to the UK industry for the short term following an EU exit and provide some time before the EEA exit for thorough negotiations with the EU and third countries (countries outside of the EU and EEA, e.g., US).

PRACTICAL PLANNING FOR SPONSORS
Although the full implications of Brexit are still unknown, a number of practical steps may be taken in the short term to begin planning for the change.

Sponsors may consider establishing an internal Brexit steering committee with multifunctional representation including a recommended minimum of regulatory affairs, pharmacovigilance, manufacturing/supply chain, legal and quality assurance representatives. The role of the committee could include:

• Carrying out a systematic review of the existing business to identify what functions currently rely on UK-based service provision in order to comply with EU requirements, e.g., UK-based EU qualified person for pharmacovigilance.

• Evaluating the anticipated business pipeline over the medium term and assessing the impact of possible Brexit scenarios on clinical development plans, regulatory strategy and commercialization strategies; considering contingency options where necessary. Examples might include planned reference member state selection for upcoming new licensing applications.

• Monitoring for any new information as Brexit negotiations progress, and communicating regular updates throughout the business.
THE UNCERTAIN ROAD AHEAD
With time since the referendum still being measured in weeks, all exit options explored here and more besides are in play. Negotiations in Brussels will be crucial to the post-Brexit picture; however, the UK has been told that negotiations can only begin in earnest once the legislative mechanism for a member state exiting the EU is triggered, i.e., invoking Article 50 of the Lisbon Treaty. Thereafter follows a period of negotiation expected to be concluded within two years.

Prime Minister May insists Article 50 will not be invoked until 2017 and so at present, a UK exit will not occur until at least 2019. In the meantime, political uncertainty will present additional challenges to negotiations, with anti-EU feeling in other member states threatening similar exit movements, particularly in France and the Netherlands. Additionally, in Scotland, a 62 percent majority voted to remain in the EU in June’s referendum. Given that the UK only narrowly avoided a breakup following the 2014 Scottish independence referendum, a second Scottish independence referendum appears likely.

Clearly, as far as European regulatory agencies are concerned, for the moment it is business as usual. This also appears true for the UK pharma industry with both AstraZeneca and GlaxoSmithKline committing to significant investment in their UK operations as recently as the end of July. A joint government-industry steering group was established in early July by then Life Sciences Minister George Freeman, to be co-chaired by AZ and GSK CEOs, to identify key priorities for the UK life sciences sector in the eventual exit negotiations with the EU.

The pharmaceutical and life sciences sector will be one of many working to influence discussions in Brussels and beyond to secure the best deal for its continued success and to maintain the UK’s reputation as a center of excellence in the field. Many eyes will be watching closely.

ABOUT CHILTERN
Chiltern, a global contract research organization, is a leading provider of clinical solutions in a variety of specialty areas and engagement models for biopharmaceutical and medical device industries. Chiltern’s team of more than 4,200, located across 47 countries, provides comprehensive Clinical Development, Medical & Scientific Affairs, Data & Analysis, Pharmacovigilance, Strategic Regulatory and Clinical Supplies services using a collaborative approach to maximize efficiency and minimize delays. Visit Chiltern.com to learn more about how Chiltern is Designed Around You®.
REFERENCES


