BREXIT STRATEGY UPDATE

Any pharmaceutical company wishing to hold EU licenses must have a legal entity registered within Europe. Pharmaceutical companies that wish to establish a new 'EU' legal entity to hold their licenses, decide on 'which country' to choose within Europe. Up until 24th June 2016 (UK referendum result day) the UK was a reasoned choice for many pharmaceutical companies wishing to establish themselves in Europe. Good flight connections, the English language, a traditionally well regarded competent health authority, and of course the current home of the European Medicines Agency (EMA). This has led to many pharmaceutical companies and subsequent Marketing Authorization Holders (MAH) historically choosing UK based legal entities to hold their European medicinal product licenses.

Under current expectations, the UK will leave the European Union on March 29th 2019 to become a so called 'third country'. The European commission is clear through Article 2 of Regulation (EC) No 726/2004 that holders of European medicinal product licenses must be established in the EU. Due to this it is likely that separate 'UK' and 'EU' legal entities will be required going forward to hold UK and EU licenses' if pharmaceutical companies wish to operate in both markets. Companies should plan for this in advance of March 2019. It should be noted that the UK government issued a white paper in July 2018 that envisages a 'softer Brexit' for the pharmaceutical industry (1). Whilst this could be welcome news for industry it is far from a certainty. Companies should plan for a hard Brexit scenario to reduce exposure and risk to medicines portfolios in line with EMA advice.

The draft EU-UK transition withdrawal agreement that will enable the UK to remain part of European processes and procedures until 2020 may buy industry more time (2). The agreement is due for ratification in October 2018. However, as of now EU companies are expected to plan in line with EMA guidance for a hard Brexit.

Any European medicinal product licenses held by UK legal entities are likely to be required to transfer the marketing authorisation holder (MAH) post Brexit. This will involve a transfer of ownership of the license from one legal entity (UK) to another (EU). Regulatory Affairs professionals typically deal with this type of change.

Conversely, EU legal entities holding UK medicinal product licenses may be required to transfer the marketing authorisation to a UK based legal entity for the Medicines and Healthcare Regulatory Agency (MHRA) to continue to accept their validity.

It is not just the legal entity changes that need to be considered as part of a so called 'hard' Brexit scenario.

European regulations also require certain persons with key responsibilities to be based in the European Union. This includes Qualified Persons for Pharmacovigilance (QPPV's) and Qualified Persons in compliance and manufacturing (QP's). Following Brexit, it is quite possible that there will need to be both QPPVs and QP's in Europe and the UK. Some UK persons may well be asked to relocate to continue supporting the European role going forward.

Manufacturing supply chains are also likely to be affected. European legislation determines that medicinal products require a formal site of 'batch release' to be based in the European Union. UK batch release sites would no longer fall within this. Similarly, any product arriving into the EU from the UK could require re-testing by an appropriate quality control/batch control site. UK specific batch release sites and UK specific product testing could also be required for products being imported from Europe.

There is also the impact of medicinal product license competent authority responsibility and assessment. Prior to Brexit the MHRA acted as the lead country in assessing European application submissions for many European medicinal application procedures. This lead role continues once the license is granted, as changes to the license will often be required in the future. When the UK is no longer in the EU the MHRA will not be able to continue to act as the lead organisation in EU procedures. One of the other countries will now need to take on the lead responsibility of being a reference member state (RMS) for the procedure to continue to be valid. As of July 2018, MHRA no-longer acts as RMS for new applications, with responsibilities being reallocated to other National Agencies.

While the European Medicines Agency (EMA) has taken proactive steps in asking European Marketing Authorisation holders to consider their positions and product portfolios carefully, very little has directly been announced so far from the MHRA beyond the White paper, which is currently under attack by high-ranking EU officials.

This all leaves pharmaceutical companies faced with an unprecedented regulatory concern affecting their portfolio of products and it is essential that they plan well in advance and consider:

- Legal Entity Requirements
- Pharmacovigilance requirements
- Manufacturing and supply chain requirements
- Changes to workload and resource

Whilst further information will be shared from both the EMA and the MHRA in due course it is important that Marketing Authorisations Holders begin planning for all eventualities now.

Call us for further details about our Brexit Strategy and implementation capabilities.

Table: Hard Brexit considerations.

Europe	United Kingdom
Regulatory Affairs	
Transfer of Ownership applications for EU Centralised, Decentralised, Mutual Recognition and National applications to Non-UK (EU) legal entities	Applications for UK National licenses (including potential Module 2-Module 5 dossier consolidation/updates)
PSMF summary variations following license transfers to new legal entities	UK National variations to add UK QC testing sites
Variations (single, bulk, grouped) to change importer/batch release site from UK-EU for EU licenses	UK National variations to add UK specific PSMF and QPPV to UK National license
Variations to change Quality Control testing sites from UK-EU for European licenses	UK National variations to add UK batch release/importation site
Orphan medicinal product designation transfer to European legal entities	Transfer of ownership applications to UK legal entities (assuming MHRA requirement)
RMS switch where UK is RMS	UK License cancellation from EU procedures
SME designation strategy and new applications where required	–
Pharmacovigilance	
EU QPPV provision (switch from UK-EU)	UK QPPV provision (for UK National licenses)
XEVMPD database entry update (or variations if following Transfer of Ownership)	UK database entry/XEVMPD equivalent if data share will not continue
EU PSMF provision (including switch from UK)	UK specific PSMF provision
–	UK specific Inspections & Audits
–	PSURs (assuming no reference to EURD list)
Compliance & Supply Chain	
EU QP and batch release provision	UK QP and batch release provision
EU Site Audits including API, Batch release, QC and Importation, Finished product & primary and secondary packaging	UK audits
EU Technical agreements and agreements between EU-UK, UK-EU	UK Technical agreements
EU GMP inspection readiness	UK GMP inspection readiness
EU Falsified medicines directive planning	UK MIA/WDA applications and variations
EU QMS	UK QMS
EU analytical method testing	UK analytical method testing (unless MRA agreed)