Diamond Pharma Services
PHARMACEUTICAL CONSULTANTS

DIAMOND PHARMA SERVICES BREXIT PACKAGE

DEPARTURES

All EU marketed products will need to be registered with a legal entity in the EU. To meet the requirements post-Brexit we offer the following Departure Service:

- **Reference member state switching and transfer of ownership applications.**
- **PSMF summary variation updates & XEVMPD.**
- **Importer batch release changes including QC sites.**

Similarly, orphan designations and SME status will need to be held by a legal entity in the EU.

- **Annex your orphan designation to Diamond Pharma Services whilst you establish your own legal entity in the EU.**
- **Diamond can help to transfer your orphan designation or SME status to your own EU legal entity.**

Diamond Pharma Services are EU regulatory specialists with a legal entity in the EU. We are continuing business as usual, but now with enhanced capability within Europe.

ARRIVALS

The UK government is yet to define the regulatory pathway for UK marketed medicines post-Brexit. However, we are UK regulatory experts with many combined years of experience dealing with MHRA. We can:

- **Help your company to be ready to maximise opportunities in UK registrations.**
- **Support your local UK regulatory requirements.**
- **Support CTA submissions in the UK.**
- **Provide the most current state of the art regulatory submissions and post-marketing life cycle management for existing UK licenses.**
- **De-risk the impact of Brexit to your portfolio of products and development programmes.**
- **Provide UK specific Pharmacovigilance including local QPPV and PSMF.**
- **Offer UK compliance solutions including UK QPs and Inspections.**
- **Cover all national post-marketing requirements.**

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Brexit Considerations for **March 2019**

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 and 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 Europe. 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.

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 (QPPVs) and Qualified Persons in compliance and manufacturing (QPs). Following Brexit, it is quite possible that there will need to be both QPPVs and QPs in the EU 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.

Brexit will also affect the responsibilities of national competent authorities for the assessment of medicinal product licenses. Currently the MHRA act 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 are often 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 country in EU procedures. One of the other countries will need to take on the lead responsibility of being a reference member state (RMS) for the procedure to continue to be valid.

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. This is potentially down to elections and in consideration of negotiations with Europe prior to March 2019.

Pharmaceutical companies are 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.**

Table 1 shows potential HARD-MAH Brexit considerations for both UK and EU. 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.

Table 1: *HARD Brexit Considerations:*

European Union	*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 EU licenses.	UK national variations to add UK batch release/importation site.
Orphan medicinal product designation transfer to EU 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.