BREXIT Impact – are you ready?

February 2019

The UK Referendum conducted on 23rd June 2016 determined that the UK will leave the European Union on the basis of the 3.8% majority, who voted in favour. Article 50 was triggered on March 29th 2017 and the 2 year period is almost up and at the moment as of 30th March 2019, the UK will cease to be a member of the EU. This will have a considerable impact on EU medicines approval since the UK MHRA acts as rapporteur for around 15% of Centralised applications and contributes approximately 30% of the EU experts available for EMA Committees. ABPI current advice is to prepare for all scenarios for Brexit - no deal and deal with implementation period.

"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."

However, in addition to this wider environmental impact, there will be specific implications for individual product licences. The EU has operated under the assumption of a 'hard' Brexit from the start, so has given frequent updated guidance to Marketing Authorization Holders on the impact e.g. publication of the EU Commission and EMA Notice to Marketing Authorisation Holders[1] and Questions and Answers[2] related to the United Kingdom's withdrawal from the European Union with regard to the medicinal products for human and veterinary use within the framework of the Centralised Procedure, have changed this situation.

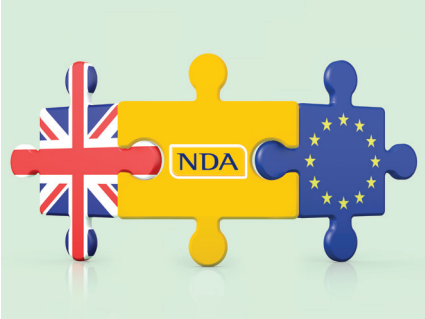
These documents urge Marketing Authorisation holders (MAHs) to address any changes required to individual licences, well in advance of the UK's departure, sage advice given the volume of consequential Marketing Authorisation variations which will need to be submitted by all EU MAHs and approved by the Agency within this comparatively short timeframe for a large number of licences:

In addition to the above-mentioned documents issued jointly by the Commission and EMA, the Co-ordination Group for Mutual Recognition and Decentralised Procedure – Human (CMDh) at the Heads of Medicines Agencies has published similar advice for similar advice for national authorised products.[3]

The MHRA has also issued guidance for UK MAHs on the impact of both an agreed withdrawal with a transition period and a 'hard' Brexit. The most recent guidance[4] has been issued in January 2019 and outlines in more detail how the MHRA will regulate medicine once the UK is outside of the EU.

How can NDA help you?

Figure 1



A strategic review of the impact of all EU product licences within a Company's portfolio is required, *see figure 1 above.* NDA is well positioned to perform this review, advise on changes required, prioritise the required changes, and project manage, prepare and submit the consequential variations in a timely manner.

This will be done via a dedicated team including specialists in European Regulatory procedures, Manufacturing & Control and Pharmacovigilance. This team is also responsible for monitoring further information updates on BREXIT impact and liaising with EMA, MHRA, and other European Regulatory agencies for specific issues. NDA offers a facility to reassign Orphan Drug Designations (ODDs) and/or Micro, Small and Medium-Sized Enterprise (SME) status which are currently established in UK and therefore impacted by BREXIT. Thus, NDA offers a broad spectrum of services to guide you through and prepare you for the BREXIT.

Areas impacted

The Q and A issued by the Commission and EMA for Centralised licences and by the Heads of Medicines Agencies for EU licences granted via Mutual Recognition or Decentralised procedures spells out the key changes that will need to be addressed, but there are other consequential changes to also be considered which follow on from these high level changes. The Agency communications are aimed at existing licences, but obviously the impact on on-going or future submissions will also need to be considered.

The major changes reflect the requirements within the EU legislation for specific tasks to be performed by sites and personnel located within the EU.

'The holder of a marketing authorisation for medicinal products covered by this Regulation must be established in the Community'.

Regulatory accountability

Marketing Authorisation Holder (MAH): according to Article 2 of Regulation (EC) No 726/2004: Following BREXIT, the UK will become a 'third country' so any EU Centralised licences which name a UK entity as the MAH must be varied to transfer the licence to an EU company. This new entity must be in a position to assume the responsibilities of the MAH. If any of these are currently sub-contracted by the UK MAH, new contracts could potentially be required.

Manufacturing, release and packaging

UK manufacturing sites for finished products will, post BREXIT, not be able to release batches of product onto the EU market. A new importing site will need to be nominated in the union (EEA) and a QP at this site will need to take responsibility for releasing the products onto the EU market. For EU licences referencing a UK finished product manufacturing site, an EU import site will need to be identified, the authorisation details amended and the QP certification in the eCTD updated.

BREXIT also impacts on release of the product onto the EU market and recognition of the quality of active substances manufactured at UK sites. Following BREXIT, active substances manufactured at UK plants will be considered imported active substances and will require certification from the MHRA that the plant manufacturing the active substance is complying with GMP that is equivalent to EU GMP.

*The qualified person responsible for pharmacovigilance **must reside** and carry out his/her tasks in the Member State of the Union (EEA).*

Any documents which reference details of the MAH and manufacturers will also need to be updated including the product information and pack. The variations will need to be carefully planned to minimise packed stock wastage.

Safety Governance and QPPV

Qualified Person for Pharmacovigilance (QPPV) / Pharmacovigilance Site Master File - Article 8 of Directive 2001/83/EC and Article 74 of Directive 2001/82/EC, say:

There will therefore be a need to identify a named QPPV that resides in the EU/EEA for each EU licence, if the named QPPV is currently based in the UK and the Article 57 database updated. Similarly, the PSMF cannot be based in the UK and details also need to be updated on the Article 57 database.

NDA consultants have extensive experience with submitting large numbers of variations for a product portfolio, assessing the changes needed, and consequences for production including supply chain, in a most effective way.

ODDs and SME status

Lastly, not only holders of product licences are impacted by BREXIT, but also holders of ODDs and/or SME status:

Orphan Designation – if this is held by a UK Company, it must be transferred to a legal entity based in the EU.

SME – UK based SMEs will need to submit a new application under an EU based regulatory consultancy with SME status or establish their own separate legal entity in the EEA which can hold the SME status.

The NDA affiliate Pharma Gateway AB established in Sweden, holds SME status and can act as an EU based "SME regulatory consultancy" for companies based outside the EU which meet the SME requirements, an option the Commission and EMA referred to in their Q&A document. Additionally, as a legal entity established in the EU, Pharma Gateway can also act as holder of ODDs.

Summary

BREXIT will have wide ranging impact on EU pharmaceuticals licences; if these include any reference to UK sites or have UK based personnel or affiliates taking critical responsibilities for the product. An urgent strategic review is needed of the impact for all EU licences with a consequent plan of changes needed, prioritisation and plan for implementation.

The recent EU and MHRA guidance has clarified the regulatory procedures that will be used in future for UK National applications post-Brexit and the approach to on-going and completed submissions which include the UK. Although it will be permitted to have an EU MAH and EU QPPV for a UK licensed product until the end of the transition period in December 2020, a UK based contact person must be nominated for each UK licensed product within four weeks of Brexit until a UK MAH is established. Provisions have also been outlined for future UK specific PIPs, ODD and SME status; although in the case of UK PIP and ODD, these are anticipated to closely follow the EU decisions. NDA can provide strategic advice and operational support for these UK specific applications.

The NDA team can support you to ensure that your company is 'BREXIT-ready'.

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References

(1) **Notice to Marketing Authorisation Holders**
http://www.ema.europa.eu/docs/en_GB/document_library/Other/2017/05/WC500226603.pdf

(2) **Questions and Answers**
https://www.ema.europa.eu/en/about-us/uks-withdrawal-eu/brexit-related-guidance-companies

(3) **Advice for national authorised products**
http://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/BREXIT/CMDh_361_2017_Rev3_01_2019_clean_-_QA_on_BREXIT.pdf

(4) **The most recent guidance**
https://www.gov.uk/government/news/medicines-and-healthcare-products-regulatory-agency-statement-on-the-outcome-of-the-eu-referendum?utm_source=d68d2244-0b58-4d08-806d-135d36a9a526&utm_medium=email&utm_campaign=govuk-notifications&utm_content=immediate)