BREXIT Impact – are you ready?

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 for negotiation is ongoing. The recent UK election may soften the approach to BREXIT, this remains to be seen, but 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.

However, in addition to this wider environmental impact, there will be specific implications for individual product licences. Up until recently both EMA and MHRA advised that it was 'business as usual' until notified, but the recent 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. As 34% of companies registered in the Community Register are based in the UK, the impact will be wide spread.

"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."

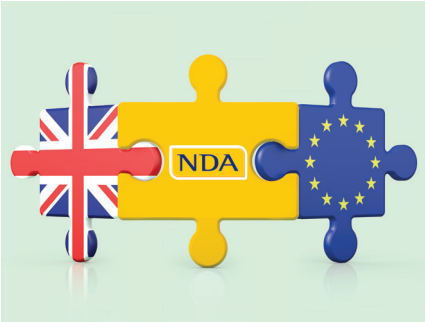
These documents urge Marketing Authorisation holders (MAHs) to address any changes required to individual licences, well in advance of the UK's departure. This is sage advice given the volume of consequential Marketing Authorisation variations which will need to be submitted by all EU MAHs and approved by the Agencies within this comparatively short time frame:

A review of the Commission's Community Register indicates that the majority (34%) of Marketing Authorisation Holders for EU Centralised licences are based in the UK, so early review of potential impact on individual product licences is recommended.

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 national authorised products**.[3] The Agency communications are aimed at existing licences, but obviously the impact on on-going or future submissions will also need to be considered.

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.

Deploying a dedicated team, including specialists in European Regulatory procedures, Manufacturing & Control and Pharmacovigilance, NDA helps ensure consistency and continuous operation. 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. Conducting a review that covers all necessary and critical aspects that Brexit will impact ensures control over the process. By also providing the operational capabilities to support companies through the necessary changes NDA provides a broad spectrum of services ensuring stability and predictability of operation.

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

Regulatory accountability

A number of accountabilities held with UK affiliates or headquarters will need to move to legal entities based in the EU. 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.

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

Entities in the UK holding SME status or an Orphan Drug Designation will be similarly impacted and these statuses must be moved to an EU based legal entity.

To support companies with these activities NDA offers services through a specialised and fully owned affiliate, Pharma Gateway AB, based in Sweden. Pharma Gateway holds SME status and can act as such on behalf of companies meeting the EC's criteria for SMEs. As an EU based legal entity Pharma Gateway also acts as ODD holder on behalf of companies.

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 the 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 for EU registered products or EU applications. UK manufacturing sites will need to comply only with UK GMP standards.

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.

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

Safety Governance and QPPV

Article 8 of Directive 2001/83/EC and Article 74 of Directive 2001/82/EC states that the QPPV must reside with an EU Member State.

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.

Organisational and vendor implications

All of the changes implied above will have different impact on the organisations and vendors used by affected companies. In some cases UK based vendors will no longer be an option to support many of the activities previously performed out of the UK.

NDA's consultants have extensive experience with handling of large amount of variations in terms of products concerned, changes needed, and consequences for production including supply chain from a regulatory perspective, in a most effective way.

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 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**
http://www.ema.europa.eu/docs/en_GB/document_library/Other/2017/05/WC500228739.pdf

(3) **Advice for national authorised products**
http://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/BREXIT/CMDh_361_2017.pdf