Brexit – Planning for regulatory preparedness and continuity of supply to the UK, outside the single market for medicines.

Tepnel Pharma Services

Abstract

The government of the United Kingdom (UK) formally notified the European council of its intent to withdraw from the European Union (EU) on the 29th March 2017. As a consequence, the European Medicines Agency (EMA) will relocate from its current base in the UK to Amsterdam in the Netherlands where it aims to take up its operations by 30th March 2019 at the latest. In conjunction with the relocation to the Netherlands, the EMA is working on the assumption that the UK will become a third country as of 30 March 2019.

It must be acknowledged that negotiations between the UK and the EU are ongoing and as yet the final outcome of those negotiations is undecided but as no Member State has previously decided to leave the EU, there is no precedent for this situation. It is vital that patients across Europe continue to receive effective, safe and high-quality medicines from within a regulatory environment that fosters innovation and the continued development of new medicines.

Therefore, planning for the effective continuity of supply chains has become one of the single biggest challenges to the pharmaceutical industry across Europe. QC release testing for the European market place has been core to Tepnel Pharma Services history and with an established and demonstrable track record in supporting large volume batch release testing, with the delivery of in excess of 400 batches per annum for a single commercial product, Tepnel is a significant partner of choice with a proven regulatory pedigree with domestic and internal regulators. With a strong regulatory pedigree, Tepnel has successfully demonstrated a commitment to patient safety over the last 40 years, driving innovation and continuous improvement principles in keeping patients safe whilst improving patient outcomes.

Regulatory Preparedness

It is possible that as of the 30th March 2019, medicinal products manufactured in the UK will be considered imported medicinal products from inside the EU. The EMA in its advice to pharmaceutical companies in advance of the aforementioned date, amongst other requirements have specified that in relation to batch control and testing, should the UK become a third country then,

"As such and in accordance with Article 51(1)(b) of Directive 2001/83 and Article 55(1)(b) of Directive 2001/82, the marketing authorisation holder will need to specify a site of batch control in the EU where each production batch can undergo (upon importation) a full qualitative analysis, a quantitative analysis of at least all the active substances and all the other tests or checks necessary to ensure the quality of medicinal products in accordance with the requirements of the marketing authorisation. Therefore, for centrally authorised medicinal products the marketing authorisation holder will need to change the location of its current UK based site of batch control to a location established in the EU."[1]

It is estimated that more than 2,600 pharmaceuticals, approved for use within the EU utilise UK based companies to provide an aspect of the manufacturing (including testing), packaging and a subsequent logistics network to export these life-saving medicines into the hands of patients.[2]

An estimated 45 million patient packs are supplied from the UK to other European countries, each month, for use in healthcare provision and improving patient outcomes. Conversely, supply chain logistics outside of the UK account for some 37 million patient packs flowing into the UK under the same regulatory framework for the very same reasons.

On the 16th January 2018, the MHRA published an update to pharmaceutical companies on preparations for the UK exiting the European Union.

In its post, the MHRA noted that it is confirmed in the Joint Report on progress during the first phase by the Government and the European Commission, issued on 8 December 2017, that "goods placed on the market under Union law before the withdrawal date may freely circulate on the markets of the UK and the Union with no need for product modifications or re-labelling; be put into service where provided in Union law, and that the goods concerned should be subject to continued oversight".[3]

However, there is currently no clear instruction from the UK as to what will be required after the withdrawal date. The UK have stated that its intention remains to secure an implementation period based on the existing structure of EU rules and regulations as quickly as possible, and to agree a deep and special future partnership. To date no such agreement has as yet been achieved and in its statement, the MHRA confirms that its "Day One and longer-term proposals – will be published when appropriate"[4] but also providing some guidance to a potential scenario whereby no agreement has been reached, the "Hard Brexit Scenario".

UK regulatory requirements after March 2019 in the event of no ongoing relationship with EMA networks.

As stated above, the UK intends to agree a time-limited implementation period with the EU, and both parties have recognised its importance. Should however there be no implementation period, MHRA's approach would be in line with the following principles:

- The European Union (Withdrawal) Bill will convert the existing EU legislative framework into UK law at the moment of exit, so there would be no sudden changes to the UK regulatory framework.
- We would be pragmatic in establishing UK regulatory requirements. We would give adequate notice and ensure that companies had sufficient time to implement any changed requirements.
- Where possible, we would be making use of the information we already have to complete administrative tasks for continuity of work and licences.
- We would ensure the minimum disruption and burden on companies as the UK exits the EU, while building on the existing relationship between MHRA and firms.

Therefore, it is not unreasonable to assume the worst case scenario and start preparations and contingency planning for a potential impact requiring point of entry testing into the UK from the EU, as per the requirements of the EMA. Therefore, preparing for and achieving regulatory preparedness to maintain continuity of supply, in both directions, should be a high level priority for all exporters of EU batch released product into the UK and vice-versa.

Change is easy

According the the MHRA, if you are considering a change in your GMP QC laboratory, that change takes less than an hour to complete and submit your change form to the MHRA. Here at Tepnel Pharma Services we are working on providing solutions for both our existing partners and anyone looking to mitigate against the future potential of the UK becoming a "Third Country" in relation to the current EU regulatory requirements around batch release testing.

We believe that it is never too soon to start planning and preparing for the potential outcome of the ongoing negotiations and that irrespective of the outcome, patient safety and improving patient outcomes has to be the primary objective.

Tepnel are happy to demonstrate our reputation in supporting this transition resulting in a risk free transition, taking the headache from the decision makers whilst ensuring supply chain continuity and patient safety.

[1] Questions and Answers 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, EMA, Rev 01, published on 1 December 2017. [2] BREXIT EFPIA survey results, EFPIA, 08/11/2017. [3] Joint report on progress during phase 1 of negotiations under Article 50 TEU on the UK's orderly withdrawal from the EU, From: Prime Minister's Office, 10 Downing Street and Department for Exiting the European Union, Published 8 December 2017. [4] https://www.gov.uk/government/news/mhra-update-to-pharmaceutical-companies-on-exit-preparations, MHRA, 2018.

Batch Release Testing with a Different Mind-set

Our approach has been embraced and embodied by a number of Tepnel's current customer base through referrals, which is a powerful indication of our commitment to understanding our partner's key business objectives, delivering key desired outcomes and business objectives.

Vested® is a business model, methodology, mind-set and movement for creating highly collaborative business relationships that enable true win-win relationships in which both parties are equally committed to each other's success.[5] The Vested methodology enables organisations to expand their understanding and application of traditional outsourcing partnerships which shift buyer-suppliers relationships from a "What's in it for Me" to a "What's in it for We" mindset and economics – truly creating win-win relationships.

As a result, we have shared with our partner's significant opportunity for cost reductions, for example, by deploying a Vested mind-set in conjunction with lean practices and principles we have facilitated a mechanism for reducing turn-around time without a compromise on quality whilst maximising efficiency.

CASE STUDY:

Proven experience in successfully managing and delivering value from a global strategic partnership during a multi-year contract period.

Project

- GMP batch release of market approved therapeutic for global markets challenges
- Product demand and contingency measures meant that there would be greater than 300 batches to be released per annum
- Within the testing schedule for each batch of product there were 13 discrete quality control tests with increasing complexity and technology requirements
- The batch testing requirements meant that there were two sets of specification limits associated with the testing requirements; Release and internal actions

Project Summary

Hologic has an MHRA and FDA approved quality control laboratory. In accordance with the requirements of Good Manufacturing Practices, batches of pharmaceutical products must be tested and certificated to meet specific specifications prior to be released for human use.

The testing requirements are designed to confirm the consistency and accuracy of the manufacturing process to ensure that high quality pharmaceutical product is made and that there is nothing that will impact on the safety of the patients who ultimately use the medicines.

Challenges

Chief among the challenges are managing the complexities of multiple analytical requirements with a desired turnaround time of not more than 20 days. Additionally, large volume manufacturing meant that a steady flow of batches for testing and subsequent release totaled to more than 300 individual batches manufactured and tested on an annual basis. The challenge of resourcing and matrixing multiple batches on a rolling basis, whilst dealing with the complications and complexities of the quality requirements associated with GMP were paramount.

Solution

Operational excellence is a philosophy deployed within the workplace where problem-solving and teamwork results in the ongoing improvement in an organization. Adopting lean principles and deploying the technique of value stream mapping, the team were able to identify minimum stock levels, trigger points and potential improvements to the management of critical materials required to achieve the testing endpoint. Through understanding and focusing on the customers' needs and desired outcomes, the team used kanban to visualise the process, eliminating waste through a reduction in WIP to ultimately manage the flow of samples through the process. Through empowerment of the team, they were able to eliminate waste, optimize the flow of value across the process and create a customer pull strategy to deliver a set of emergent measures through quality, cost reduction and efficiency gains.

Results

Stakeholders	Scientists	Procurement	HOLX
Starting Point	- TAT ≤20 days - GMP Quality	Fixed price per batch	- Volume - Profit X
Innovation Outcomes	- TAT ≤10 days - GMP+ Quality	Cost savings per batch	- Volume stet. - Value creation
Emergent Measures	- Receipt to CoA down 50% - ↑ productivity - Enhanced quality (Negative NC)	Up to 40% reduction in per batch price	- Up to 30% ↑ profit (c.f. actual time ↑ NC's) - Hours claw back - Reward Potential - Trust

By deploying innovation through operational excellence, within a Vested Outsourcing business model, a win-win situation was created which sees the desired outcomes and associated rewards achieved by all the parties.

Conclusion

Whilst the future remains unsure, progress has been made but the spectre of a worst case scenario still looms.

Irrespective of this patient safety and improving patient outcomes remains the preserve of the pharmaceutical industry in both the UK and the EU. Attaining regulatory harmonization lies at the heart of both the MHRA and EMA but recognizing, planning for and mitigating against a worst case scenario should not be disregarded.

[5] Source: Used with permission. Vested®. www.vestedway.com. Vested Outsourcing, Inc.