Preparing for the Post-Brexit Clinical Supply Chain

September 2018

GLOBAL CLINICAL SUPPLIES GROUP

For clinical trial sponsors and clinical supply vendors with research in the United Kingdom (UK) and/or the European Union (EU), changes are coming. With the UK scheduled to leave the EU on March 29, 2019, understanding how this will affect the clinical supply chain is critical to supporting ongoing research. While political negotiations are ongoing, and the exact outcome is unclear, the research industry needs to prepare now.

This article outlines the discussion that took place at the GCSG conference in Atlanta in April 2018 as a precursor to the ongoing conversation anticipated at the GCSG European Knowledge Forum in Barcelona, October 23-25, 2018.

Brexit: The Situation

While the UK voted to leave the EU on June 23, 2016, the UK government did not invoke EU treaty Article 50 (a formal withdrawal request) until March 2017. Official negotiations between the European Parliament and the UK government began in June 2017. To date, no official deals have transpired.

Even though the date is set for the UK to officially leave the EU, there is the potential for a transition period, whereby all existing trade regulations would remain in effect until the end of 2020. However, nothing has been officially agreed upon, and the trade status of the UK post-Brexit could range from a no-deal "hard Brexit," whereby the UK and EU would follow World Trade Organization rules; to a new trade deal, called "soft Brexit," which could leave trade regulations unchanged, or something in-between.

The UK is the first country to leave the EU, and any agreement will require a majority vote of EU countries, as well as ratification by the UK parliament. Once the UK officially leaves the EU it has stated that it will no longer be a part of the EU Customs Union, and therefore would be able to negotiate trade deals with countries independently. Additionally, if the UK also leaves the European Economic Area (EEA) it will be leaving the single market and regulatory union.

Given that the UK wants to maintain a close relationship with the European Medicines Agency, (EMA) as well as remain part of European research and development initiatives, they will likely continue to mirror EU regulations and align with the EMA. However, without definitive decisions from their respective governments and regulatory bodies, regulatory agencies are advising clinical trial sponsors and clinical supply vendors to prepare for the worst-case scenario, a hard Brexit. Therefore, it is increasingly important to understand how the clinical supply chain will function in a variety of outcomes.

Possible UK Regulatory Status Post-Brexit

3rd Country with no deal or European Free Trade Association (EFTA) State	• UK facility's EU GMP compliance must be declared (including any testing performed in UK facility) and vice versa • UK QP certificates not recognized by EU and vice versa
EFTA State + European Economic Area (EEA) Membership or Mutual recognition agreement (MRA) Country	• UK GMP equivalent to EU GMP • UK QP certificate can be leveraged by EU QP and vice versa • QP certification required upon receipt in EU and vice versa
New Deal	May include: • UK GMP equivalent to EU GMP • UK QP certificate valid in EU • No further QP certification required upon transfer to EU

Clinical Supply Chain Considerations

In order to mitigate risk, it is important for companies to consider several key areas: supply chain, packaging/pre-production, process systems, quality/regulatory, personnel and trade. Each of these areas have multiple risks to evaluate, some of which may overlap. To help companies get ready, this article will look more closely at some specific issues related to the clinical supply chain, materials flow, clinical trial applications, quality and compliance and costs.

Material Flows

In preparing for Brexit, clinical supply operations need a detailed understanding of how their supply chain comes together, starting from the API (active pharmaceutical ingredient) all the way to ownership of materials and supplies. It will be necessary for companies to know if materials will require sourced services, where those services will be conducted as well as where specific products are manufactured and sourced. Understanding these specifics of the materials flow process will not only help the company's Qualified Persons (QPs) but will also be financially beneficial in case of a hard Brexit, where goods and services could have additional tariffs and will need to be declared appropriately.

Another consideration for the materials flow process is knowing facility capacity to support planning for shipping between the EU and UK. Potential delays associated with customs and inspections in a hard Brexit scenario could impact the ability to ship and receive clinical supplies.

Companies may want to set up supply facilities in both the UK and the EU, making dual batch release sites optimal and efficient, or consider a mitigation strategy where batches are stored in distribution warehouses on either side for more predictable distribution. A company may also need to update or change any interactive response technology (IRT) post-Brexit to reflect their new physical models.

Clinical Trial Application

Any clinical trial applications (CTAs) submitted over the next year need to keep Brexit in mind. Pre-planning will save companies time and money post-Brexit due to a decreased number of changes or application updates based on new regulatory guidelines. CTAs will also need to include any potential amendments for ongoing protocols, such as label or facility changes.

The location of QP certification and release, whether in the UK, the EU, or both, will also need to be addressed in the CTA. Additionally, companies need advanced knowledge of which countries have marketing authorization for any commercial non-investigational products included in the CTA.

Quality and Compliance

To ensure appropriate audits and quality agreements are in place, sponsors and vendors need to strategize with quality assurance teams and review facilities. Ensuring all measures are in place is especially critical if a company plans to utilize a new facility pre/post-Brexit while supporting ongoing clinical trial continuity.

Understanding the role of QPs is also important to enable clinical trial success. QPs are required to release in the EU, and even countries with mutual recognition agreements with the EU, such as Switzerland, have to import any clinical products. A QP is required to attest to the quality of a product, certify that the product is in compliance with, or equivalent to EU good manufacturing practice (GMP) standards, the information in the CTA, and the product specification file. Overall, QPs are also responsible for ensuring the supply chain is compliant with EU GMP standards.

Important questions to ask (and why they matter)

Are project supply chain maps and lead times in place?

Creating project supply chain maps that include details surrounding the IMP, required components and comparator sourcing (if applicable) enables the identification of any potential gaps in a supply chain.

Determining the required lead time for facilities to supply each other in the UK and EU in advance can help avoid delays and mitigate any potential risk to UK facilities with EU supplies (and vice versa).

Do Operations teams in UK and EU facilities have appropriate processes and ongoing demand surveillance mechanisms?

Key internal teams that are responsible for accepting, scheduling and managing the flow of projects need ready access to current and pending workload information and visibility into available operational capacity. This is particularly important to inform and facilitate the timely transfer of projects and/or specific responsibilities between facilities.

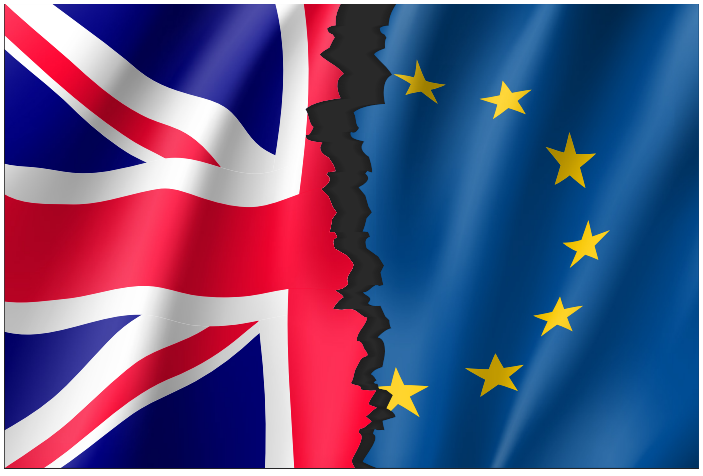
Today, nearly 70% of clinical trials in the EU are using UK QPs for certification. In the case of a soft Brexit, the UK will recognize QP certification from the EU and it can be presumed, but still unknown, that the EU will, in turn, recognize UK QP certification. But in the case of a hard Brexit, QP certification may be required in both the EU and the UK. Companies should discuss with QPs the legalities of future trade agreements, as well as review current technical agreements and QP-to-QP agreements. It is important for companies to recruit and certify QPs now to ensure capacity and meet any new regulations.

Other important quality and compliance considerations include product specification files, documentation flow and ensuring investigational medicinal products (IMP) are declared in the both the EU and the UK to prepare for post-Brexit requirements and additional audits.

Brexit Costs

While regulators recommend preparing for the worst-case scenario, there will be costs involved for sponsors and vendors. Some costs will only be one-time costs, such as amending CTAs, or changing an IRT strategy. However, other costs will be longer term, for example, opening a second distribution facility to have one in the UK and the EU, as well as hiring QPs to support each facility.

Other long-term costs may be related to tariffs and taxes. Companies should work with indirect tax accountants to understand the implications of Brexit on duty and value added tax (VAT). Duty tax can range up to six and a half percent but can be avoided with good duty management systems. It must be kept in mind that while using a duty management system can help avoid some taxes, it can also raise a company's profile within a country's Customs authorities, therefore, companies need to have robust compliance policies in place.



VAT is a consumption tax that can range from 19 to 27 percent of declared value and is collected at the point of importation. Sponsors and vendors should know where they are VAT-registered and must carefully complete export documentation. Any errors in VAT can cost up to 200 percent of the original tax amount, so understanding how VAT will impact the clinical supply chain post-Brexit is part of a sound financial strategy.

Preparing for a Complex Future

Preparing for the unknown environment of regulations and trade after the UK leaves the EU is complicated, and no single solution will work for every company. Conducting a thorough supply chain risk assessment is advisable to inform future operations. Decisions may need to be made at a protocol level, which means companies need to evaluate each protocol step and strategize potential changes.

Getting ready for a hard Brexit will require an integrated strategy and innovative solutions. Companies must work collaboratively across departments to understand the fiscal implications as well as regulatory, quality and clinical supply chain challenges.

Clinical trial sponsors and clinical supply vendors with current or planned studies in the UK and/or the EU need to stay informed as Brexit negotiations progress. Both the EMA and the UK Medicines and Healthcare Products Regulatory Agency (MHRA) post regular updates online.

Additional information on how Brexit will affect the clinical supply chain will be a topic of discussion at the fifth annual Global Clinical Supplies Group (GCSG) 2018 European Knowledge Forum, October 23-25, 2018 in Barcelona, Spain: https://www.rsvpbook.com/event.php?574055.

GCSG would like to thank 4G Clinical for sponsoring our 2018 US Conference in Atlanta and the development of this important industry article.
Learn more about 4G Clinical at www.4gclinical.com