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Brexit and the future landscape for clinical trial supplies in the UK and Europe

Brexit caused a seismic shift in the way in which the United Kingdom (UK) and Europe (EU-27) dealt with each other and how the rest of the world traded with the EU-27 and the UK. From the moment the UKs leave referendum result was announced, the clinical trial industry shifted uncomfortably in their seats pointing to the fact that up to 70% of clinical trials were QP certified within the UK and 1500 clinical trials had the sponsors registered address within the UK.

The supply routes for everything from fish, wine and sausages to critical lifesaving drugs (both commercial and clinical) were set to be impacted. The long-awaited trade agreement was announced at the eleventh hour, but was it enough to prevent supply chain disruption?

Early indications were not good as shipments were held in customs for inexorably long periods, with local customs officials unable to process shipments and unaware of some of the exceptions that could have been granted under the legal framework of the withdrawal agreement.[1]

Let's take a look at the political background of Brexit and its impact on clinical trial supplies in the UK and the European Union (EU).

Introduction

At 11pm GMT on 31st January 2020, after 47 years of membership, the United Kingdom left the European Union.

This was the beginning of the last act in the protracted Brexit Saga which began with the UK referendum of 23rd June 2016, in which given the choice (Should the United Kingdom remain a member of the European Union or Leave the European Union?) 51.9% of the UK public voted to exit, stage left. The Brexit date itself passed rather inconsequentially with a further 11 months of the transition period still to run and the small matter of a trade agreement to be negotiated.

At the eleventh hour the UK and EU finally reached an agreement on the myriad of customs, political and governance issues and the trade deal was published on 24th December 2020. The Trade and Cooperation Agreement (TCA) was put in place to detail future trading relations between EU, Great Britain (GB) and Northern Ireland (NI). At 11pm on 31st December 2020 the UK's transition period for leaving the EU ended and a new trading relationship under the provisionally agreed TCA began; the trade deal was officially ratified by an EU vote on 28th April 2021. Here's an overview of the impact that the UK leaving the EU will have on the future of clinical trials in both regions.

The Trade and Cooperation Agreement

The TCA sets out preferential arrangements in areas such as trade in goods and in services, digital trade, intellectual property, public procurement, aviation and road transport, energy, fisheries, social security coordination, law enforcement and judicial cooperation in criminal matters, thematic cooperation and participation in Union programmes.[2]

One aspect that both negotiating parties agreed was mutually beneficial for all was that the agreement delivered zero tariffs and zero quotas on all goods that comply with the appropriate rules of origin.[3]

With the TCA running over 1400 pages, this article does not aim to provide a complete and comprehensive content review. We'll focus on how the TCA relates to medicinal products and show how the changes, that have ensued since 01st January 2021, will affect clinical trial supply chains and regulatory requirements within the UK and EU.

The TCA does include a number of Technical Barriers to Trade (TBT) Annexes that were initiated to reduce bureaucracy between the UK and EU as the future relationship evolves. Annex TBT-2 specifically addresses Medicinal Products; however, it covers only 4 real pages of text and was widely regarded as a very thin agreement.

The scope of the agreement includes:

- **marketed medicinal products for human or veterinary use, including marketed biological and immunological products for human and veterinary use**
- **advanced therapy medicinal products**
- **active pharmaceutical ingredients for human or veterinary use**
- **investigational medicinal products**

Whilst the objectives of the agreement are:

- **to facilitate the availability of medicines in each Party's territory**
- **to set out the conditions for the recognition of inspections and for the exchange and acceptance of official GMP documents between the Parties**
- **to promote public health by safeguarding patient safety and animal health and welfare, as well as to protect high levels of consumer and environmental protection, where relevant, by promoting regulatory approaches in line with the relevant international standards.**

Fundamentally, Annex TBT-2 is an agreement to recognise GMP inspection reports conducted by either the EU or the UK to eradicate the need for duplication of inspections by either Party. The remainder of the text within Annex TBT-2 has language in relation to exchange of information, regulatory cooperation and suspension of arrangements.

As the EU and UK do not routinely inspect Investigational Medicinal Product (IMP) manufacturers outside of Europe (as that responsibility falls upon the Qualified Person), the applicability of Annex TBT-2 to IMPs is somewhat limited.

What has changed to IMP supply chains since 1st January 2021?

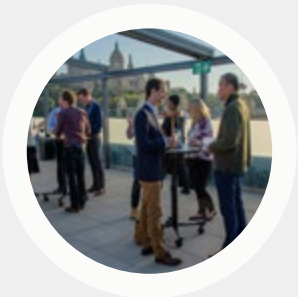
Site of EU Importation

If a facility within Great Britain (England, Wales or Scotland) was the site of importation for an EU clinical trial, this will no longer be the case. As the UK (GB and NI) is no longer part of the EU at the end of the transition period, facilities located within Great Britain could no longer act as the site of EU importation. One would imagine that to be a fairly simple step change, but here the small matter of the UK vs Great Britain rears its head. Through the Brexit negotiations, there was a desire by all parties that a hard border on the island of Ireland be avoided. Article 185 of the EU Withdrawal Agreement (Northern Ireland Protocol) put provisions in place to ensure that NI would follow EU laws even after the end of the transition period. Consequently, a facility within the territory of NI can act as an EU importation site, but those located within GB can no longer be an EU importer.

> **CLINICAL TRIAL IMPACT:** If you have a multi-country EU clinical trial and the site of EU importation was a facility within GB, this will need to be changed to an EU-27 member state or Northern Ireland facility.

Site of Qualified Person (QP) certification

Seemingly from the outset of the Brexit negotiation process, the EU negotiation team took a hard stance that QP certification would need to be undertaken with a remaining EU-27 country. This stance is supported by the existing directives surrounding clinical and commercial drug products (2001/20/EC and 2001/83/EC respectively). The UK negotiators reportedly sought to establish a Mutual Recognition Agreement that would avert the need for duplication of certification and testing regarding drug products moving between UK and EU. The European Medicines Agency (EMA) actively indicated to industry that no such mutual recognition agreement would be forthcoming and, in a joint technical notice published in July 2020, stated: "Sponsors of all ongoing trials need to establish a QP in the EU. Failure to do so could in the worst case result in discontinuation of trial treatment and thus jeopardise trial participants' safety."[4] Consequently, akin to the need to change the EU importation site, sponsors were also required to identify a suitable QP based within the EU-27 or NI. This also led to a need to update Clinical Trial Application (CTA) forms (section D.9.2), and if the batch release site was recorded within the Investigational Medicinal Product Dossier (IMPD) "manufacturers" section, this too would need to be updated.



Many of the UK-based clinical trial service providers, who previously acted as EU import sites or QP sites, moved early to avert impacts on supply chains by advising clients to make the required changes and, if not already in place, to establish facilities within the EU-27 or NI.

> **CLINICAL TRIAL IMPACT:** If conducting a multi-country EU clinical and the site of QP Certification were a facility within GB, the QP certification site would need to be changed to a EU-27 member state or NI facility, and associated CTA forms and IMPDs would need to be updated.

Importation and Qualified Person Certification for ongoing and future trials within UK/GB

The UK regulatory authority (Medicines and Healthcare Regulatory Authority (MHRA)) took a pragmatic approach to the lack of recognition of UK QP certification. Instead of forcing a recertification of clinical trial materials coming into the UK from EU, the MHRA have given a grace period until 31st December 2021, where no changes will be required. An EU QP-certified clinical trial material can ship directly to a GB clinical site with no additional oversight during this period.

Thereafter, commencing 01st January 2022, a new system will be introduced: "If you are the Sponsor of a UK clinical trial using IMPs imported into Great Britain from countries on an 'approved country for import' list (initially, all EU and EEA countries) you will require a UK Manufacturing and Import Authorisation (MIA(IMP)) holder to put in place an assurance system to check these IMPs have been certified by a Qualified Person (QP) in a listed country, before release to the trial."[5]

Under this new system, there are two options to supply GB clinical sites: a direct-to-site shipment or the use of a distribution hub within the UK.

The hub option is considered to be the safer of the two to ensure regulatory compliance as the need to ensure QP certification before dosing will be much easier to control in such cases.

It should be noted that if Clinical Trial material is shipping from NI to GB, then no additional oversight is needed.

> **CLINICAL SUPPLY CHAIN IMPACT:** No immediate impact for the remainder of 2021. Thereafter, if you intend to move Clinical Trial Material from an EU-27 country to GB, you will need to employ the services of a GB-based facility to act as overseer of that process and put in place appropriate agreements to cover those arrangements.

Who can certify my clinical trial material (CTM)?

In writing this, it became apparent just how complex this would be to an outsider looking in; the table below should provide context to what's written above and at the same time give the reader a valuable, easy to digest, point of reference.

		Location of QP			
Storage site of CTM	**Clinical Trial site**	**EU**	**GB**	**NI**	**Comments**
EU-27	EU-27 (and NI)	Yes	No	Yes	GB QP no longer recognised by EU
EU-27	GB	Yes*	Yes*$	Yes	*Subject to UK MIA IMP verification after Jan 2022 $Would require EU and UK QP certification
GB	GB	No	Yes	Yes	EU QP could not oversee GB import
GB	EU-27	Yes!	No	Yes!	!EU/NI QP could only certify after EU importation
NI	GB	Yes*	Yes	Yes	*Subject to UK MIA IMP verification after Jan 2022
NI	EU-27	Yes	No	Yes	GB QP unable to certify stock held in NI

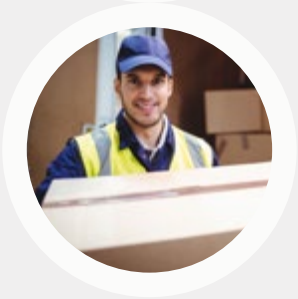
Sponsor or legal representative must be established within the EU

In the joint technical notice published in July 2020, EMA reminded sponsors: "according to Article 19 of Directive 2001/20/EC, the sponsor of a clinical trial or a legal representative must be established in the EU."[4] The notice went on to state that failure to comply could result in corrective action being taken by Member State competent authorities.

However, whereas the Northern Ireland Protocol allows a QP in NI to provide certification for EU, a sponsor or their legal representative cannot be established within NI; they must be located within an EU-27 country.

CLINICAL TRIAL IMPACT: Sponsors are required to amend their EudraCT Application form, updating sections B.1 and B.2.

Movement of materials from GB to EU and EU to GB



Whenever an international shipment is made, even if there is no actual purchase, the parties responsible for reporting the shipment, to the government in each country, are called the Exporter of Record (or Seller) and the Importer of Record (or Buyer).

To better understand the flow of the clinical supply chain, we should start by identifying the key players in the chain:

- **Consignor (shipping site): Person or Party that is physically shipping the commodities**
- **Exporter of Record: Person or party responsible for compliance with export regulations**
- **Importer of Record: Party responsible for import regulation compliance, accuracy of the information submitted to customs and/or other agencies and for the payment of duties and import value added tax (VAT) taking legal and regulatory responsibility of the goods being shipped**
- **Consignee (receiving site): Person or Party that physically receives the commodities**

In the pre-Brexit world, materials moved freely between the UK and the other EU member states as part of the European free market. Goods imported from outside the EU also qualified for free circulation within the EU once all import formalities had been completed within the country of physical importation where import duty and any other customs charges had been paid.

As an example, if a USA-manufactured CTM were imported to the UK prior to Brexit, the UK importing site would have been responsible for import duties and taxes incurred at the time of import, but thereafter, materials would be able to circulate freely.

With the end of transition, borderlines were redrawn and supply chains changed, seemingly overnight. The UK became a non-EU country (a third country) when the Brexit transition period ended on 31st December 2020. The obligation for customs clearance of goods moving between GB and the EU-27 commenced from 1st January 2021.

Considering the same example of a USA-manufactured CTM imported to the UK after Brexit:

Upon UK importation, the shipment would be liable to pay import duties against the full shipment value.

If a portion of the shipment were then required to be distributed within the EU, it would need to be imported to an EU-27 member state and be subject to further import duty charges.

This sudden change has forced even greater scrutiny on supply chains and distribution plans to avoid double-dipping on duty charges.

Value Added Tax

As Benjamin Franklin said, "The only two certainties in life are death and taxes". That quote is appropriate post Brexit as when it comes to moving materials within the EU and GB the taxmen will come looking for their pounds (or euros).

Import VAT is a tax paid on goods purchased from another country outside the EU. European VAT Directives has set the minimum standard VAT rate at 15%. The EU-27 Member States are thereafter free to set their standard VAT rates, with this being on average 21%. The UK VAT rate is currently set at 20%.

The EU's duty relief and the World Trade Organization Pharmaceutical Agreement ensure that pharmaceuticals do not incur any import duty. Placebo, however, is considered food with a duty rating of 12.8% (EU) and 12% (UK).

When taking the above into consideration, the following example provides evidence why it is important that sponsors, or their designated exporter/importers, get the customs declaration process right, or it could be costly:

Shipment 1 No Split	Shipment 2 (Split) Active and Placebo
Total Value = £200,000. (Single line does not differentiate between active value and placebo value)	Total Value = £200,000 (£170K: Active, £30K: Placebo). Active pharma (tariff code 3004900000) No Duty
Placebo (tariff code 2106909260) is liable to 12% duty = £24,000	Placebo (tariff code 2106909260) is liable to 12% duty = £3,600
VAT = Duty amount + (invoice value) x 20%	VAT = Duty amount + (invoice value) x 20%
VAT= £24,000 + ((£200,000) x 20% = £ 44,800)	VAT = £3,600 + ((£200,000) x 20% = £ 40,720)
Total to pay: £68,800	**Total to pay: £44,320**

Regardless of the customs declarations, there are mechanisms in place to recover accrued VAT.

- **UK**

Her Majesty's Revenue and Customs (HMRC) guidance published in May 2019 confirming…

"HMRC has categorically stated that only the owner of the goods should be the importer of record for the purposes of reclaiming the import VAT, either via its UK VAT registration or via the VAT refund procedure for traders established outside the EU."

- **EU-27**

Twenty-seven individual countries all with their own customs procedures and rulings. Typically, only the owner
of the goods can reclaim VAT by submitting an application according to the specific rules of the EU Member States concerned.

EORI

EORI stands for "Economic Operators Registration and Identification number". Businesses wishing to trade must use the EORI number as an identification number in all customs procedures when exchanging information with Customs administrations.

Since January 2021 (end of transition period) – Non established companies need an EU EORI number to make import (and export) declarations when they import into an EU member state. A customs declaration with a UK EORI number is valid for UK imports only.

Conclusion

Brexit has brought fundamental changes to clinical trial supply chains. The good news is that in the majority of cases, Sponsor companies and logistics providers put the patient first and acted in a timely manner to minimise disruption and ensure that IMPs are delivered to patients when they are needed.

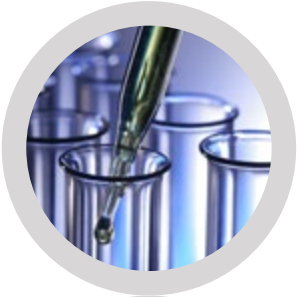
There are future challenges to overcome as new rules for supply chain oversight become effective in 2022 for the UK; and, there remains a risk that UK and EU legal requirements may diverge over the course of time making the conduct of trials in both the UK and EU a less attractive proposition.

Whether the UK remains a popular location for clinical trials may well hinge on the successful roll out of the EU Clinical Trial Regulation (CTR). A smooth implementation of the CTR would decrease regulatory divergence while further harmonising and simplifying the process of conducting trials in multiple EU member states. This could leave the UK as the outlier, with a separate regulatory route required to conduct trials there compared with the rest of the EU-27.

References:

1. https://www.theguardian.com/politics/2021/feb/04/cancer-drugs-binned-because-of-brexit-red-tape-mps-hear
2. https://ec.europa.eu/info/relations-united-kingdom/eu-uk-trade-and-cooperation-agreement_en
3. https://www.gov.uk/government/publications/agreements-reached-between-the-united-kingdom-of-great-britain-and-northern-ireland-and-the-european-union/summary-explainer
4. Joint technical notice by the European Commission, EMA and HMA. July 2020

   Ares (2020) 3624454/ Technical notice to sponsors regarding continuous compliance with the EU Legislation for clinical trials following the withdrawal of the United Kingdom from the EU
5. Importing Investigational Medicinal Products (IMP) from countries on a list to Great Britain https://www.gov.uk/government/publications/importing-investigational-medicinal-products-into-great-britain-from-approved-countries/importing-investigational-medicinal-products-imp-from-countries-on-a-list-to-great-britain



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