Specialist Pharmacy Service

National Pharmacy Clinical Trials Advisory Group

Operational Implication of UK Exit from the EU – Guidance for NHS Pharmacy Clinical Trial Sites

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Version 1
September 2022

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Introduction

The Pan UK Pharmacy Working Group (PWG) for Advanced Therapy Medicinal Products (ATMPs) acts as an expert and informed body to support the activities of UK Pharmacies to facilitate ATMP usage. The group consists of pharmacists from across the UK that specialise in the governance, prescribing, administration and monitoring of ATMPs. The aims of the group are to promote good practice, identify and resolve pharmacy issues to maximise the effectiveness and development of services for hospitals to administer advanced therapies. The Pan UK PWG for ATMPs has a clinical trials subgroup, which identified a need for consistent regulatory compliant advice regarding importation of ATIMPs following the UK's exit from the European Union.

This document has been written by members of the Pan UK PWG for ATMPs but as its content relates to all investigational medicinal products, it has been ratified by The National Pharmacy Clinical Trials Advisory Group (NPCTAG).

NPCTAG was established in its current form in 2010. The group's objectives are to provide advice on matters relating to clinical trials to NHS pharmacy services, the National Institute of Health Research Clinical Research Network, and to support education & training of pharmacy staff. The NPCTAG is a Specialist Pharmacy Service network.

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Operational Implication of UK Exit from The EU for NHS Trial Sites, including Advanced Therapy Investigational Medicinal Products (ATIMPs)

Background:

From 31st January 2020, the United Kingdom (UK) ceased to be a member of the European Union (EU). The transition period related to importation of Investigational Medicinal Products (IMPs) was finalised on the 31st December 2021. The new arrangements have several significant impacts on the supply chain of IMPs.

The main changes are:

- UK Qualified Person (QP) Certification is no longer recognised in the EU/EEA
- EU/EEA QP Certification is still recognised in the UK, provided:
- EU/EEA QP Certification must be confirmed by a UK MIA(IMP) holder under UK QP oversight during importation

This guidance has been written by members of the Pan UK Pharmacy Working Group for ATMPs but it focusses on the importation of all IMPs for use in a UK clinical trial. Where an IMP is certified within the UK, arrangements remain unchanged. Specific regulatory and QP requirements for ATMPs have been summarised in "The Role of a Qualified Person within Advanced Therapy Medicinal Products (ATMPs)" document.

IMPs certified by an EU/EEA QP can be used for GB clinical trial supply provided the country where the IMP is certified appears on the approved country for import list (initially all EU and EEA countries). As part of the importation process, a UK QP must have oversight of a system that verifies appropriate QP certification has occurred in the listed country ("supply chain oversight") prior to the IMP being made available to the GB trial site.

The aim of this document is to highlight the key changes related to importation of IMPs or comparators certified in a country on the "approved country for import" list to be incorporated into pharmacy SOPs where required.

General Information: IMPs imported into GB from countries on "Approved country for import" list for use in trials delivered in the UK

1. Trials that are opened and running prior to 1st Jan 2021:

   The trial Sponsor must submit a substantial amendment to add or change any IMP manufacturing, importation, or certification site relevant for supply of IMP to GB sites for an ongoing trial. This will include the details of the UK Manufacturing and Import Authorisation (MIA (IMP)) holder performing the "supply chain (QP) oversight" role.

2. Trials in set up:

   Information about the supply chain participants will be submitted as part of the CTA and IRAS application. This must include the MIA(IMP) holder that is responsible for the QP oversight activity.

3. Agreements:

The Sponsor must have all necessary technical agreements in place with all members supporting the supply chain, and this remains a Sponsor responsibility irrespective of the change in legislation. There may be specific requirements which mandate a multi-way agreement including a trial site, for example, where an (AT)IMP has an extremely short shelf life and must be shipped under quarantine prior to certification. In these circumstances, because the certifying and importing MIA(IMP) holders and Sponsor must rely on the site to establish appropriate controls to stop the (AT)IMP being made available for use prior to completion of the necessary import activities, in this circumstance, an agreement outlining the various responsibilities of all parties would be beneficial.

What Is the Oversight Process?

For UK clinical trial supply, where QP certification is performed in a listed country, confirmation that the IMP has been certified must be obtained by the UK MIA(IMP) holder responsible for the import of that IMP as stated in the CTA. The IMP does not require re-certification; the UK QP is responsible for ensuring a suitable system is in place to verify that QP certification has occurred in the EU/EEA country. The routine tasks relating to verification of QP certification may be delegated by the QPs named on the UK MIA(IMP) to appropriate personnel operating with their quality system.

A Sponsor may perform QP oversight themselves if they are the holder of a UK MIA(IMP) which allows the relevant activity. Alternatively, they may outsource this verification to a third party who holds a UK MIA(IMP). In any event, the MIA(IMP) holder performing the activity must be stated in the CTA.

Receiving A Shipment: Evidence of QP Oversight

There is no current regulatory guidance on acceptable evidence of QP Oversight for clinical trial sites. It is a sponsor responsibility to ensure that the appropriate UK QP verification has taken place. However, pharmacy clinical trial sites are recommended to gain some evidence to ensure that they have undertaken appropriate due diligence.

Evidence which may be provided to a site could be:

- Confirmation from Sponsor that a particular batch has been supplied via the authorised route
- A 'Certificate of Importation' issued by the UK MIA(IMP) holder stating the appropriate checks have been performed
- Best practice would include confirmation for each shipment, although confirmation on a batch-by-batch basis may be appropriate where a UK distribution hub is used

Supply Scenarios:

1. **The IMP is manufactured in UK**
   The IMP is manufactured by a UK MIA(IMP) holder stated in the CTA, and QP certified. Trial sites will get a QP certificate via the Sponsor as usual.

2. **The IMP is manufactured and imported from a third country (a country not on the approved list for import) directly into the UK**

Each batch will need to be certified at the UK MIA(IMP) holder stated in the CTA by a UK QP prior to release. Trial sites will get a QP certificate via the Sponsor as usual.

3. **The IMP is manufactured and/or imported from a country on the "approved list for import"**
   Oversight of a QP named on a UK MIA(IMP) is required (the QP can delegate this task to appropriately trained personnel working under the MIA(IMP)).

   a. **Supply directly from Manufacturer to a UK clinical trial site**
      The IMP batch must remain in quarantine at the trial site, until Sponsor confirms that the UK QP oversight process has taken place for this product. In this scenario, appropriate controls will likely have been established by the Sponsor, which may include a technical agreement between all parties involved. It may also be necessary for the UK MIA(IMP) holder performing the oversight to satisfy themselves that a site has appropriate controls in place to prevent the IMP being made available until this process is complete.

      If the QP oversight process is completed prior shipment of the IMP, then these arrangements may be unnecessary. There may still be a requirement to confirm shipping conditions have been suitable maintained before making the IMP available to the trial site, however.

   b. **Supply to a UK storage and distribution "Hub"**
      The IMP batch will be released to site after the UK MIA(IMP) holder has completed the oversight process confirming QP certification has occurred in the listed country. The Sponsor will provide confirmation that this has taken place to the local site. There is no need to quarantine the IMP upon shipment receipt, although it would be good practice to confirm this process has been followed on receipt of the IMP as discussed above.

NORTHERN IRELAND

EU QP certification of products manufactured in EU/European Economic Area (EEA) will also enable supply of IMP to Northern Ireland either directly or via Great Britain without requiring the UK QP (or delegate) oversight process. IMP supplied to Northern Ireland (e.g., QP certified in the EEA) may subsequently be onwardly shipped to GB, also without requiring the QP oversight process as outlined below.

IMPs coming to GB from Northern Ireland do not require UK QP (or delegate) oversight when:

a. EU QP certified IMPs are supplied from EU/EEA for use at Northern Ireland clinical trial sites and are then supplied to GB
b. IMPs are QP certified by a Northern Ireland MIA (IMP) holder

IMPs going to Northern Ireland from GB do not require UK QP (or delegate) oversight when:

c. IMP is UK QP certified in UK for use at Northern Ireland clinical trial sites
d. IMP is EU QP certified in EU/EEA for use at Northern Ireland clinical trial sites

Table 1. Summary of supply scenarios:

Where has been the IMP manufactured	Requirement	Supply chain	NHS Pharmacy
Great Britain	Each batch will need to be certified by a UK QP named on the MIA(IMP) for the site of certification stated in the CTA	GB manufacturer to GB site	NHS pharmacies will get a QP certificate via the Sponsor as usual.
Approved country for import list - EU/EEA listed countries	Confirmation of QP certification in a listed country by (or under the oversight of) a QP named on a UK MIA(IMP).	Supply directly from EEA manufacturer to a UK clinical trial site	IMP kept in quarantine by receiving site until Sponsor confirms the oversight process required for importation has been completed
		Supply from an EEA manufacturer to a UK storage and distribution "Hub", subsequent supply from hub to UK site (storage hub must be named as a storage location on the MIA(IMP) holders authorisation).	The IMP batch will be released to site after the UK MIA(IMP) holder has completed the oversight process
		Supply from EEA manufacturer to NI site	No checks required; IMP can be onward supplied from NI to GB also with no additional checks.
Northern Ireland	IMPs are QP certified by a Northern Ireland MIA (IMP) holder	Northern Irish manufacturer supply to any UK site	No checks required; IMP is already QP certified in UK
Third country (not on the approved country for import list)	Each batch will need to be certified by a UK QP on entry to UK	Third country manufacture to UK MIA(IMP) holder for certification	NHS pharmacies will get a QP certificate via the Sponsor as usual.

References:

1. MHRA Guidance, Importing investigational medicinal products into Great Britain from approved countries.

2. Catapult. Cell and Gene Therapy. Guidance Document. Cell and Gene Therapy Catapult Guidance on the development and marketing of ATMPs in the UK and EU at this position post-BREXIT. Date: 7th December 2021. Updated on 26th January 2022.

3. Regulation 43, of The Medicines for Humans Use (Clinical Trials) Regulations 2004 (as amended), UKSI 2004/1031.

List of approved countries for clinical trials and investigational medicinal products: https://www.gov.uk/government/publications/importing-investigational-medicinal-products-into-great-britain-from-approved-countries/list-of-approved-countries-for-clinical-trials-and-investigational-medicinal-products

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