



# 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

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## 1. Introduction

Cell and Gene Therapy Catapult (CGTC) was established to advance the growth of the United Kingdom's Advanced Therapy Medicinal Products (ATMPs) industry. Our role is to create powerful collaborations which overcome challenges to the advancement of the sector. We are a team of experts covering all aspects of advanced therapies. Applying our unique capabilities and assets, we collaborate with academia, industry, and healthcare providers to develop new technology and innovation.

By helping developers to understand the guidance and legislation for ATMPs, CGTC's regulatory team provides expert support, from the development and conduct of clinical trials, through to registration for commercialization.

The United Kingdom (UK) is now a third country with respect to the European Union / European Economic Area (EU), and the Medicines and Healthcare products Regulatory Agency (MHRA) is the UK's standalone medicines and medical device regulator. Industry will adapt to the diverging and additional regulatory requirements for the UK when compared to the EU, due to Brexit. Regulatory procedures and pathways for developers of ATMPs in the UK need to be understood to maximise potential for developers. CGTC will keep abreast of the regulatory requirements for the UK and the EU, to identify opportunities and develop strategies arising from any divergence.

For the time being, the current [EU scientific guidelines for ATMPs](#) and ATMPs are, in the main, still applicable in the UK. However, the MHRA is now responsible for regulatory assessments on all medicines and medical devices in accordance with current UK law.

This document aims to describe the current situation with an emphasis on the UK regulatory requirements; it provides consolidated information on the UK environment to enable developers to operate within the new landscape in order to promote ATMP development in the UK.

The legislative and government agency requirements are dynamic and will evolve as the UK EU Exit policy becomes more mature. The information in this document should be used as a guide which will be updated as legislative changes are brought into force.

## 2. Summary of legislative changes as a result of the UK leaving the EU

The UK is now a third country with respect to the EU and as such there have been substantial regulatory changes which must be considered in the development, manufacture, and supply of ATMPs (licensed or for clinical trial). In addition, [the Northern Ireland \(NI\) Protocol](#), an agreement between the UK and the EU, necessitates that NI continues to follow EU law. NI has in effect remained in the EU's single market for goods whereas Great Britain (GB) (England, Scotland and Wales), have left the EU's single market for goods. As a result, NI is required to comply with EU Medicines, Blood, tissues and cells, and ATMP legislation, creating a dichotomy between GB and NI requirements for ATMP manufacture and supply.

The following sections detail the impact of Brexit on Good Practice (GxP) related activities for developers situated within GB. Developers within NI will predominately operate under EU rules for the time being.

### 2.1 Tissues and cells (and blood)

Requirements for tissues and cells, and blood, intended for use in patient treatment (e.g., bone or corneal grafts, stem cell transplants or blood transfusion) derive from two suites of EU Directives<sup>1</sup> - transposed into UK law - which set out minimum standards for quality and safety. These are:

- The Human Tissue (Quality and Safety for Human Application) Regulations (SI 1523/2007) (as amended). Tissue and cell procurement, testing, processing, storage, distribution, import and export of human tissues and cells for patient treatment are licensed by the [Human Tissue Authority](#), and
- The Blood Safety and Quality Regulations 2005 (SI 2005/50) (as amended). Blood Establishments are licensed by the MHRA under.

Where starting materials for ATMPs are human tissues and cells, they must meet these standards in respect of procurement and testing. Procurement must be from pre-selected donors that have been evaluated as suitable based on their medical history and tested for mandatory infectious disease markers, under the appropriate licences. The HTA and MHRA have agreed that collection of blood as a starting material for an ATMP can be performed under either a Tissues and Cells or Blood Establishment Licence<sup>2</sup>.

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<sup>1</sup> EU Tissues and Cells Directives (2004/23/EC) and EU Blood Directive (2002/98/EC) including Commission implementing directives

<sup>2</sup> Regulation of blood as a starting material for ATMP manufacture ([HTA Website](#); accessed November 2021)

Import or export of tissues and cells used as starting materials for ATMPs are also licensed by the HTA (see section 2.1.1 below). Further guidance should be sought [directly from the HTA](#) on whether other HTA licensable activities are applicable for any steps involved in the handling of tissues and cells prior to them being manufactured into medicines, if required.

Following EU Exit, four statutory instruments<sup>3</sup> amended the legislation above to provide a set of UK-wide rules for (separately) tissues and cells, and blood; within these a small number of provisions will apply to NI only, which must continue to meet the requirements of the Directives.

The Human Tissue Authority (HTA) and the MHRA will continue to be the Competent Authorities in NI and GB for the regulation of tissues and cells, and blood, respectively.

There are no changes to the substance of the quality and safety standards which remain largely the same across the UK. Detailed requirements for licensed establishments are set out in the HTA's [Guide to Quality and Safety Assurance of Human Tissues and Cells for Patient Treatment](#) (the Guide) as implemented by HTA Directions 001/2021.

The key changes in relation to import/export provisions and traceability using the Single European Code for tissues and cells are outlined below.

### **2.1.1 Importing and exporting tissues and cells<sup>45</sup>**

#### **GB - EU/EEA**

GB establishments that send (export) or receive (import) tissues and cells to, or from, a country in the EU/EEA now need a HTA licence that covers these activities (in line with the requirements for other third countries); this applies to tissues and cells for both human application (e.g., grafts or transplants) and starting materials for ATMPs. Licensed importers are responsible for ensuring that imported tissues and cells meet equivalent standards of quality and safety and must be able to provide evidence of this through written documentation and agreements.

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<sup>3</sup> The Blood Safety and Quality (Amendment) (EU Exit) Regulations 2019 (SI 2019/4)  
The Human Tissue (Quality and Safety for Human Application) (EU Exit) Regulations 2019 (SI 2019/481)  
The Blood Safety and Quality (Amendment) (EU Exit) Regulations 2020 (SI 2020/1304)  
The Human Tissue (Quality and Safety for Human Application)(Amendment)(EU Exit) Regulations 2020 (SI 2020/1306)

<sup>4</sup> UK Transition Guidance ([HTA website](#) accessed 18/11/21)

<sup>5</sup> Brexit: business guidance: Quality and safety of human organs, tissues and cells ([gov.uk](#) accessed 18/11/21)

Establishments in EU Member States are also required to apply third country import/export requirements to movement of tissues and cells between GB establishments and EU Member States. Although they must implement the requirements of Commission Directive (EU) 2015/566, each EU Member State has different requirements and processes for the import of human tissues and cells from a third country. It should be noted that import licence application processing may take up to 90 days in many European Member States. In addition, for some Member States, agreements may be required to be in place between importing and exporting establishments before the licence application can be made.

It is therefore recommended these are planned in advance to prevent substantial delays, and that developers seek early engagement with relevant Competent Authorities.

### **GB - NI**

GB establishments receiving tissues and cells from establishments in NI are not subject to any changes. Similarly, GB establishments do not require an export licence to send tissues and cells to establishments in NI. Therefore, for GB establishments, the movement of tissues and cells between NI and GB has the same requirements as other movement within the UK – establishments may however need to provide information and enter into agreements as outlined below.

### **NI - GB**

NI establishments need to treat suppliers in GB in accordance with the relevant EU regulations on third country (non-EU) suppliers. Therefore, an establishment in NI receiving tissues or cells from GB will require an import licence and associated import agreements and documentation.

NI establishments can continue to send tissues and cells to GB without an export licence.

### **NI – EU/EEA**

Tissues and cells transported from NI to the EU/EEA are not considered to be imports. Licences granted to establishments in NI to distribute tissues and cells are recognised in the EU<sup>6</sup>.

[Guidance](#) and [application forms](#) can be accessed from the HTA's website.

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<sup>6</sup> [European Commission Notice to Stakeholders](#); Withdrawal of the United Kingdom and EU rules in the field of substances of human origin (blood, tissues and cells, organs) REV2

### **2.1.2 Traceability and labelling for tissues and cells**

GB is no longer required to follow the Single European Code (SEC) (Commission Directive (EU) 2015/565). Establishments in GB must continue to ensure the traceability of tissues and cells, and can use the traceability systems in place before the introduction of the SEC. Establishments in GB may use the SEC if they wish to do so, however the European Commission no longer include GB Tissue Establishments in the EU Tissue Establishment Compendium.

NI establishments are required to continue using the SEC in traceability and labelling of tissues and cells, subject to established exemptions. Detailed requirements for allocation and application of the SEC can be found in the HTA's [Guide](#). NI establishments are included in the [EU Tissue Establishment Compendium](#).

Tissues and cells shipped to EU Member States will need to conform with the requirements of the SEC. For tissues and cells from GB, responsibility for allocation and application of the SEC should follow the requirements for imports in the receiving Member State.

## **2.2 Clinical trials**

Clinical trials to be conducted in the UK are significantly impacted by Brexit. The following guidance should be considered when applying for a clinical trial.

### **2.2.1 Registration of Clinical Trials**

Any clinical trial in the UK must be registered on a publicly accessible database. As a result of Brexit, the MHRA do not have access to the EU-Clinical Trial Register. The Health Research Authority (HRA) has made a long-term commitment, in its ['Make It Public'](#) transparency and openness in health and social care research strategy, for the registration of clinical trials on behalf of sponsors and researchers. Until a system is in place clinical trials should be registered on an established international register such as [ISRCTN registry](#) or [ClinicalTrials.gov](#).

### **2.2.2 Legal Representative**

For UK trials, the MHRA will continue to accept the Sponsor/Legal Representative located in the UK or a country on the approved list available on the [MHRA's website](#). This list currently includes EU/EEA countries.

Clinical trials conducted within the EU require the Legal Representative located within the EU; by now most sponsors and developers should have transitioned their Legal Representative from the UK to the EU for EU applications for trials. This named



position should be changed via submission of a substantial amendment to the relevant EU/EEA Competent Authorities.

## **2.2.3 Supply chain considerations**

### **2.2.3.1 Qualified Person (QP) Certification**

#### **EU Batch Certification QP responsibilities**

QPs, Quality and Pharmacovigilance, for Batch Release and Pharmacovigilance responsibilities, respectively, must now be situated in the EU. Certification of a batch of medicinal product by a UK QP now requires recertification in the EU.

A QP for pharmacovigilance (QPPV) can reside and operate anywhere in the UK or EU/EEA for UK nationally authorised product. Where the QPPV does not reside and operate in the UK a national contact person for pharmacovigilance who does reside and operates in the UK is required.

#### **UK Batch Certification QP responsibilities**

QP certification will continue to be required to use an investigational medicinal product (IMP and ATIMPs) in a UK, NI, or GB clinical trial<sup>7</sup>.

QP certification performed in GB will enable the supply of IMP to NI until further notice. QP certification performed in the EU/EEA will also continue to enable supply of IMP to NI via GB until further notice.

The recognition of a QP for the certification of investigational medicinal products, Regulations 43(2A) and 43A and 43A of the SI 2004 No 1031 as amended, refers to a list of countries approved for batch control (QP certification) and import of IMPs into GB from outside of the UK which allows the import without recertification by a UK QP.

Therefore, a QP named on a UK manufacturing and import authorisation for IMPs (MIA(IMP)) is not required to recertify an IMP on importation to GB when there is evidence to show that it has been QP certified in a listed country. The listed country QP certification should refer to the relevant UK clinical trial.

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<sup>7</sup> Regulations 13(2) and 43 of the Medicines for Human Use (Clinical Trials) Regulations 2004 (as amended) [Legal Representative Approved country list](#)

### 2.2.3.2 Batch testing for Clinical Trial Materials<sup>8</sup>

#### EU requirements

Currently, batch testing may be performed outside the EU, including in GB or NI, where this is performed to standards equivalent to those required by the UK and EU, and will remain the case after 31 December 2021.

#### UK requirements

Batch testing performed outside the UK will be accepted if performed to standards equivalent to those required by the UK. The NI protocol will not affect this, unless changes come about in the future.

CGTC will keep abreast of the changes following on from the end of this period.

#### **Batch Release and Quality Control Testing considerations for ATIMPs from UK for clinical trial in the EU**

The requirements can be found in Article 13.3(b) of Directive 2001/20/EC, and in Article 11 of Directive 2003/94/EC.

Quality Control (QC) or batch testing is a requirement for ATIMPs and should be performed in accordance with the approved clinical trial specifications. For ATIMPs that are imported into the EU, the importer may rely on the results of analysis from a non-EU laboratory and there is no need to repeat the testing on import. However, the test laboratory must be compliant with EU GMP as part of the process of supply chain assurance and the QP Declaration.

If the QC laboratory in the third country is not compliant with EU GMP then the ATIMP would require import testing, as per the requirements described in EU GMP Annex 16.

For batch release, the QP responsible for final certification of the finished ATIMP must ensure compliance with any specific expectations for GMP as per the approved CTA and IMPD registered details. This includes confirmation that the correct version of the documents within the submission are available to the QP where any substantial amendments have been submitted.

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<sup>8</sup> Refer to regulations 13(2) and 43 of the Medicines for Human Use (Clinical Trials) Regulations 2004 (as amended)

## **Batch Release and Quality Control Testing considerations for ATIMPs from EU for clinical trial in the UK**

For UK clinical trial using ATIMPs imported into GB from countries on the ‘approved country for import’ list, (this list is available on the [MHRA website](#), currently includes all EU and EEA countries and will be reviewed every three years), no retesting of ATIMPs is required.

The UK Manufacturing and Import Authorisation (MIA(IMP)) holder is required to put in place a quality assurance system, which must be overseen by a QP to check the ATIMPs have been certified by a Qualified Person (QP) in the listed country, before release to the UK trial. The routine tasks relating to verification of QP certification in a listed country may be delegated by the QP named on the UK MIA(IMP) to appropriate personnel operating within their MIA(IMP) quality system. The QP named on the UK MIA(IMP) that is responsible for this verification process may be resident in the UK or a listed country.

Any manufacturing activity or importation from a non-listed country must be certified by a QP who resides in the UK.

MHRA guidance published on 16 March 2021, confirms the UK’s continued recognition of EU batch testing will be reviewed no later than 30 December 2022, with any changes being subject to a 2-year notice period.

### **2.2.4 Import and Export changes**

#### **2.2.4.1 Import to the UK**

Up to 31 December 2021, IMPs may be supplied direct from the EU/EEA MIA(IMP) holder to the ongoing GB trial site without the GB MIA(IMP) oversight process. Therefore, as a clinical trial sponsor there is no need to submit a substantial amendment if the sponsor retains an existing UK IMP release site for the UK trial and includes an EU/EEA release site for trials in the EU/EEA.

From January 2022 sponsors of a trial with sites in the UK need to ensure they have a Manufacturer’s Authorisation for IMPs (MIA(IMP)) for the importation of an IMP for a UK clinical trial. The MIA(IMP) holder must ensure they have the appropriate quality assurance procedures for the import, including verification of QP certification in the member state, which must be overseen by the UK MIA(IMP) QP before the IMP can be used in the clinical trial. The IMP does not require recertification.

There are two routes for IMPs to be received into the UK from a listed country for use in UK clinical trials following QP certification by the listed country MIA(IMP) holder:

- 1) direct to the clinical trial site or
- 2) via a UK storage and distribution ‘hub’.

There should be written agreements between all relevant organisations (Sponsor, MIA(IMP) holder, distributor etc) which details responsibilities of the parties.

Following a recent update by the MHRA, this is now applicable to authorised medicinal products (non-investigational and/or unmodified) that are used in clinical trials. It is also a requirement for authorised medicines sourced from NI to GB.

Sponsors in this position will need to submit a substantial amendment to include the details of the UK MIA(IMP) holder performing this supply chain oversight.

#### **2.2.4.2 Export from the UK to the EU**

The export of investigational medicinal products manufactured or packaged in the GB to the EU, requires a UK MIA(IMP). This authorisation is required even if only part of the manufacturing (e.g., repacking, for example as part of blinding activities) is performed in GB.

A substantial amendment to include the details of the UK MIA(IMP) holder performing this supply chain oversight will be required in the relevant EU member state.

#### **2.2.5 Safety reporting requirements**

The UK's MHRA does not have access to the EMA EudraVigilance database and systems and therefore all expedited safety reports to the MHRA will need to be through UK portals. For suspected unexpected serious adverse drug reactions (SUSARs), submission must be made via either:

- the [ICSR Submissions portal](#) which replaces the EudraVigilance website (EVWEB)
- or the [MHRA Gateway](#) which replaces the EudraVigilance Gateway

The ICSR Submissions portal can only allow consecutive submission of a single report, whilst the MHRA Gateway has the functionality to allow a bulk of several single reports to be sent in one submission.

Additionally, establishments using tissues and cells as starting materials must be aware of the requirements for reporting serious adverse events and reactions related to the procurement and testing of those materials. In the UK, reports can be made to the HTA via their [online portal](#).

#### **2.2.6 Genetically Modified Organisms (GMOs)**

The legislation relating to the control of the deliberate release of GMOs has not been updated and there are no current changes as a result of Brexit. CGTC will monitor the UK legislation for future updates.

### **2.2.7 EU Clinical Trial Regulation and UK Combined Review**

The new EU Clinical Trial Regulation (CTR) (Regulation (EU) No 536/2014) to be implemented January 31<sup>st</sup>, 2022, will not apply in the UK since the implementation occurs outside of the transition period. The current Statutory Instrument for clinical trials in the UK is The Medicines for Human Use (Clinical Trials) Regulations (SI 2004 No 1031) (as amended).

In the UK, the clinical trials approval process is also changing. All clinical trial submissions for the UK must be submitted directly to the MHRA and from 1 January 2022, all new clinical trials of investigational medicinal products (which includes ATIMPs) will benefit from a more streamlined and efficient clinical trial approval service. This new service combines regulatory and research ethics committee review, referred to as the 'combined review service'. It involves a single application route with a coordinated ethics and regulatory review to set timeframes leading to a combined UK decision on a clinical trial.

The service is open now to all CTIMP sponsors and applicants. To register, make a submission, or to get more information, please refer to the [Health Research Authority](#) website.

Please note: CTIMP applications via combined review must be submitted using a new part of the Integrated Research Application System (IRAS) and should not be started in the standard part of IRAS. Furthermore, it will not be possible to create new applications for CTIMP trials on the standard part of the IRAS system from 14 December 2021.

Clinical trials for the EU will be progressed through the EU Portal via the CTIS (Clinical Trial Information System) in line with the new CTR from 31<sup>st</sup> January 2022.

### **2.2.8 Northern Ireland**

A phased approach is being applied to NI in line with the NI Protocol. IMPs can be supplied from GB to NI with a pragmatic approach to applying European Union (EU) rules on importation requirements. Apart from importation requirements, IMPs used in clinical trials in NI must follow the [EU acquis](#) as per the NI Protocol. This is as set out in the draft EU Unilateral Declaration in the Withdrawal Agreement Joint Committee.

On 22<sup>nd</sup> December 2021, the MHRA published updated information relating to changes in the NI protocol for regulatory importation requirements to allow for unfettered access of medicines and IMPs. Regulatory importation requirements will be

removed for all medicines moving between Great Britain and Northern Ireland from 1 January 2021. This is not time limited and is in response to the supply issues in NI as a result of Brexit. One of the conditions for eligibility of the ‘unfettered access route’ is that the marketing authorisation (MA) must be established in NI.

Another change relates to access of new novel medicines. For new novel medicines that licenced through the centrally authorised route (CAPs), companies will be able to make use of a new bridging mechanism to ensure their product is licensed for the whole of the UK if the MHRA licences this product before the EMA. This is to allow unfettered access of medicines to NI.

EU regulatory requirements are still applicable to NI to ensure that there is no hard border on the island.

In order to provide certainty and stability as discussions continue between the UK and EU, the Government has set out that it will continue to operate the Protocol. Existing arrangements continue in force, including extending the specific arrangements, easements and/or grace period until further notice. CGTC will keep abreast of any changes.

The Government will ensure that reasonable notice is provided in the event that any of these arrangements are to change, to enable businesses and citizens to make appropriate preparations.

### **2.3 ATMP classifications**

The definitions of individual classes of ATMPs remains unchanged and the classification of ATMPs in the UK will be undertaken by the MHRA in accordance with the legislation and current guidance.

Accordingly, ATMPs will continue to be classified as either:

- gene therapy medicinal products
- somatic cell therapy medicinal products
- tissue engineered products
- combination products

### **2.4 UK Marketing Authorisations (MA)**

Prior to Brexit, an application for a MA for ATMPs, would have been through the centralised route whereby a single MAA is submitted to the EMA; on approval the MA allowed the holder to place the ATMP on the market in all EU member states. The centralised procedure is no longer relevant to GB since it is not part of the EU, and as such the EMA MAA accelerated regulatory pathways (prime scheme, conditional

marketing authorisation, exceptional circumstances, accelerated assessments and compassionate use) are also not applicable in GB.

In GB, ATMPs will now be approved for supply nationally by the MHRA according to the same principles that previously applied i.e. marketing authorisation applications for ATMPs will be assessed in accordance with the general provisions in place for the licensing of medicines, taking their specific requirements into account. Guidance on the requirements for MAA of ATMPs is available on the MHRA website [Great Britain Marketing Authorisation Applications for Advanced Therapy Medicinal Products](#).

Data, traceability, exemptions from licensing, packaging, and post-authorisation requirements remains unchanged from the current EU requirements and have been transposed into UK law.

In NI ATMPs will continue to be regulated according to the EMA's Centrally Authorised Procedure; in addition to this, in order to ensure availability of new novel medicines that licenced through the centrally authorised route (CAPs), a new bridging mechanism will be in place to ensure the new novel product is licensed for the whole of the UK if the MHRA licences this product before the EMA.

## **2.4.1 UK expedited approvals**

The MHRA has introduced accelerated assessment procedures and new routes of evaluation, that are applicable to ATMPs, to prioritise access to new medicines that will benefit patients. These streamlined procedures ensure that the UK remains favourable for the authorisation and marketing of ATMPs and other medicines.

### **2.4.1.1 European Commission (EC) Decision Reliance Procedure**

For a period of two years from 1 January 2021, when determining an application for a GB MA, the MHRA may rely on a decision taken by the European Commission (EC) on the approval of a new MA in the centralised procedure. This route – the EC Decision Reliance Procedure (ECDRP) - is available to MAs approved via the centralised procedure.

The intended operation of the ECDRP is submission of the Marketing Authorisation Application (MAA) to the MHRA immediately on receipt of a positive Committee for Medicinal Products for Human Use (CHMP) opinion, although applications can be submitted any time after the approval of a European Union Marketing Authorisation. The MHRA aims to determine the GB MA as soon as possible after EC approval.

MHRA have published [guidance](#) on how to apply for marketing authorisation via this procedure.

### **2.4.1.2 Great Britain Accelerated Approval**

The MHRA has introduced an accelerated assessment procedure aimed at expediting the MAA approval to ensure the availability of medicines for patients in GB. The MHRA aims to reach an opinion on marketing authorisation applications (MAAs) within 150 assessment days of filing an application.

### **2.4.2 Conditional Marketing Authorisation**

A national Conditional Marketing Authorisation (CMA) scheme for new medicinal products in GB is another route for the registration of ATMPs in GB. This can be used in cases where insufficient data is available at the time of registration and grant with the conditions that the data will be obtained at an agreed future date. This procedure allows the access to good quality medicines to patients within the UK for medicinal products that can fulfil an unmet medical need, such as serious and life-threatening diseases and where there is no satisfactory treatment methods available or where the product offers a major therapeutic advantage.

### **2.4.3 Rolling Review**

The MHRA have also confirmed the introduction of the ‘Rolling review’ procedure for new active substances which could also be applicable to ATMPs. The ‘Rolling review’ procedure involves submission of the eCTD dossier in separate parts for a pre-assessment, instead of the standard submission consisting of a full consolidated eCTD dossier. It is an efficient way to review the dossier as the data is generated in order to expedite approval.

## **2.5 UK Paediatric Investigation Plans (PIP)**

In accordance with the [Human Medicines Regulations](#) (EU Exit) Regulation, a PIP is a requirement and the results from an agreed PIP must be included in the UK MAA. The MHRA takes decisions relating to UK PIP and waivers, modifications and compliance statements to support paediatric market authorisation.

The format and submission procedure for PIP applications to the MHRA is discussed in [separate published guidance](#). Applicants should include information relevant specifically to the UK, particularly with respect to any areas of unmet therapeutic need that this product intends to cover.

As confirmed by the [MHRA](#), case-by-case discussion should always be considered for any paediatric submissions to the MHRA that do not fall into any of the prespecified criteria.



Parallel submission of PIPs to EMA and MHRA is strongly supported to allow robust parallel assessment and alignment of the agreed paediatric plans across jurisdictions.

Submission to MHRA is through a dedicated PIP portal in the MHRA Submission platform.

Currently, NI is following the EU's system for paediatric medicines development including agreement of EU paediatric investigation plans (PIPs) or waivers.

## **2.6 Orphan drug designation**

If the orphan drug designation is granted, the medicinal product will benefit from up to 10 years of market exclusivity from similar products in the approved orphan indication. An additional 2 year exclusivity will be granted where results of studies from a PIP are included in the product information.

Pre-marketing authorisation orphan designation is not required in GB anymore and the orphan designation will now be determined at the time of the MAA or via a variation application.

If a medicinal product has been designated orphan in the EU under Regulation (EC) 141/2000, a GB orphan MAA can be made under regulation 50G of the Human Medicines Regulation 2012 (as amended). A UK-wide orphan MAA can only be considered in the absence of an active EU orphan designation.

If a UK-wide orphan marketing authorisation is granted and the medicinal product subsequently receives EU orphan designation, the market authorisation holder (MAH) would need to submit a variation to change this to a GB orphan MA.

## **2.7 MHRA Submission Platform**

Submission of regulatory applications for the UK is through the MHRA Submission Portal. This is used for submissions including MAA, Post Approval licence submissions, PIP, and Safety reports. There are two user reference guides which contain step by step guidance on the processes: [Gaining access to MHRA Submissions](#) and [Managing users on MHRA Submissions](#)

The Common European Submission Platform (CESP) will continue to be applicable to all of the other EU countries.

## **2.8 MHRA advice meetings**

### **2.8.1 Scientific advice**

Scientific advice from the MHRA is available at any stage of the initial development and can be useful for ATMPs particularly, for clinical trial application (design and conduct) and before and after an MAA is submitted. The advice usually consists of a meeting with the MHRA where regulatory data, pharmacovigilance and information for the MA dossier can be discussed.

There have been no changes in the processes for requesting scientific advice because of Brexit; typically such services are provided by a country's health authorities for clinical trials, MAAs and post-approval changes, this is the case for the UK's MHRA.

The process usually consists of the developer/sponsor/marketing authorisation holders providing documentation prior to the meeting, with scientific information on the proposed medicinal products and the questions or clarifications required. During the meeting, sponsors may give an extended presentation, the MHRA discuss any raised points and provide their responses for the submitted information. The minutes of the

advice meeting are documented, agreed and formalised. Scientific advice can be given for quality, non-clinical and clinical aspects of the medicinal product.

The MHRA's responses to questions posed during scientific advice meetings are based on the documentation submitted at the time and don't account for any future changes and developments in scientific knowledge or regulatory requirements. The MHRA specifies that scientific advice is not legally binding for any future application of the medicinal product, either on the part of MHRA or the sponsor/developer.

The EMA also has a procedure to provide scientific advice for MAA using the centralised route.

### **2.8.2 MHRA Innovation Office**

CGTC Regulatory Affairs work with sponsors and developers to provide guidance and assistance with bringing ATIMPs to the marketplace by providing regulatory services, including how best to utilise the MHRA services with respect to scientific advice and innovation office meetings. CGTC coordinate and provide support for regulatory scientific advice.

CGTC work within the frameworks offered not only by the MHRA in the UK, but also the EU and international markets such as the US. Advice can't be taken as indicative of any future agreed position.

The MHRA Innovation Office provides free and confidential expert regulatory information, advice, and guidance to organisations of all backgrounds and sizes based nationally or internationally, on innovative medicines, medical devices, and manufacturing processes.

The MHRA's Innovation Office also hosts the Regulatory Advice Service for Regenerative Medicine (RASRM). RASRM is a 'one stop shop' for research and development professionals, offering a single point of access to advice and guidance from multiple regulatory bodies (including HTA, HRA and MHRA) on the regulation of regenerative medicines. The Advice Service is accessible at any time via an innovation office query form. The MHRA may provide a response to the query within 20 days or request a meeting to further discuss the query. The meeting is an opportunity for developers to utilise the expertise and experience of the MHRA and can be particularly useful for ATMP development programs.

## **2.9 Early Access to Medicines Schemes (EAMS)**

Another service offered by the MHRA which could be used for ATMPs is the Early Access to Medicines Scheme (EAMS) for medicines that do not have a marketing authorisation. The scheme aims to provide patients with life threatening or seriously debilitating conditions access to medicines where there is a clear unmet medical need. The MHRA gives a scientific opinion on the benefit/risk balance of the medicine, based on the data available when the EAMS submission was made. The opinion lasts for a year and can be renewed. Developers can make an application for a promising innovation medicine designation which can support the eligibility for the EAMS.

## **2.10 Innovative Licensing and Access Pathway (ILAP)**

The MHRA have introduced a new scheme following on from Brexit. The 'Innovative Licensing and Access Pathway' scheme provides novel approaches to accelerate the time from development, marketing, and ultimately patient access of new medicinal products. The MHRA and developers work with various stakeholder partners, for example NHS England, NHS Improvement, National Institute for Health and Care Excellence (NICE), The All Wales Therapeutic and Toxicology Centre and the Scottish Medicines consortium, to enhance access of these medicines.

ILAP is open to commercial and non-commercial developers in the UK and internationally and can be utilised by developers of ATMPs if the product meets the defined criteria namely

- a) the medicines are used to treat life-threatening or seriously debilitating condition, or there is a significant patient/public health need,
- b) the medicines are innovative (ATMPs, or new chemical or biological entity or novel drug device combination) are being developed in a clinically significant new indication for an approved medicine, and
- c) medicines for rare disease and/or other special populations such as neonates and children, elderly, and pregnant women.

It comprises of an Innovation Passport designation, a Target Development Profile (TDP) and provides applicants with access to a toolkit to support all stages of the design, development, and approvals process.

## **2.11 Good Practice**

The UK is currently still in accordance with 'Eudralex Volume 4, Part IV Guidelines on Good Manufacturing Practice for Advanced Therapy Medicinal Products' and EU Good Distribution Practice (GDP) guidelines; however it is understood that more emphasis will be placed on the Orange Guide: Rules and Guidance for Pharmaceutical Manufacturers and Distributors 2017 and the Green Guide: Rules and Guidance for Pharmaceutical Distributors 2017 and the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S) Guides to good manufacturing practice for medicinal products in future.

The MHRA has its own database of GMP licences and certificates since it no longer has its access to the EudraGMDP database; therefore, the inspection outcomes of the MHRA are not reflected in the EudraGMDP database and reference should be made to the MHRA database.

## **2.12 Biological Standards and Control**

The MHRA has provided guidance with respect to the certification of batches of immunological medicinal products or medicinal products derived from human blood or plasma products (including plasma pools). These will now be carried out by the National Institute for Biological Standards and Control (NIBSC). For medicinal products derived from human blood or plasma imported from the EU, wholesale dealers in GB that import the biological medicines from the EU will be required to check that each batch has an appropriate NIBSC or Mutual Recognition Agreement certificate before placing on the market in GB.

## **2.13 Medical Devices**

The new 'Medical Device Regulation' for the EU has not been transposed to UK law and is not applicable to GB. The new the In-Vitro Medical Device Regulations will also not be applicable in GB when it becomes effective in the EU. In GB, a new procedure is now available for manufacturers to market medical devices in the UK. Medical devices need to be registered with the MHRA, however, the current system for classification still applies.

The UK Notified Bodies are no longer able to issue CE certificates (other than for the purposes of the "CE UKNI" marking, which is valid in NI) and the EU no longer recognises UK Notified Bodies. The EU MDR already applies in NI and EU IVDR will apply in NI from 26<sup>th</sup> May 2022.

For manufacturers that are based outside of the UK wishing to place a medical device on GB market, a single UK Responsible Person is required who will take responsibility

for the device in GB should be appointed. The MHRA have provided guidance for manufacture and distribution of medical devices within the UK on their [website](#).

## **2.14 Authorised Medicinal Products**

### **2.14.1 Supply of Authorised Medicinal Products for GB market**

Medicinal products that hold a MA from an EU/EEA country can be supplied to the UK without the need for retesting or recertification. In the first instance the country must be on the country for import list as stated on the [MHRA website](#). The Wholesale dealer's licence of the importer should be varied to reflect the new process which entails listing a nominated responsible person for import. The responsible person nominated for import (RPi) will be responsible for checking that the products are imported from a country on the list and that it is certified in line with Article 51 of Directive 2001/83/EC. This is only applicable to licensed medicines and is not applicable to unlicensed or medicines that are imported to be subsequently exported. This is now a requirement for authorised medicinal products that are used in clinical trials (non-investigational and/or unmodified).

A recent update from the MHRA requires a RPi for medicines sourced from NI to GB.

The UK QP is responsible for ensuring that the Quality Systems are in place to for the operations of the RPi.

All medicinal products manufactured in the UK for export to the EU/EEA country will require recertification by an EU QP.

### **2.14.2 Supply of Authorised Medicinal Products for the EU market**

The QP of the manufacturing and importation authorisation holder is responsible to certify that each batch of medicinal product intended to be placed on the EU market was manufactured in accordance with EU GMP requirements and the marketing authorisation.

Each batch imported into the EU has to 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. This requirement has not changed as a result of Brexit, the only changes is that the UK is now a third country and for UK import to EU the requirements as for a third countries now applies to the UK.

### **2.14.3 Supply of Authorised ATMPs for the EU market**

In the case of an authorised ATMP imported from a third country (UK), the imported ATMP batches **have to be** retested upon importation into the EU. The batches have to be certified for release by an EU QP.

For countries where a Mutual Recognition Agreement (MRA) with the EU exists, then the QP certifying the imported batch can rely on controls conducted in that country (batch release testing in accordance with the terms of the marketing authorisation) where the product has been manufactured and tested.

Reliance on controls conducted outside of the EU (where no relevant MRA on GMP is in place, such as the UK) is exceptional and cannot be applied beyond the specific scenarios described in the GMP Guideline for ATMPs. The exemption from EU retesting of ATMPs granted in the MA require the following conditions:

- 1) limited amount of material available, or
- 2) a short shelf-life, and
- 3) the testing in the third country is conducted in GMP-certified facilities.

This exceptional exemption is primarily foreseen for imported patient specific ATMPs (e.g., autologous product).

#### **2.14.4 Post marketing**

Centrally Authorised Products (CAPs) have been ‘grandfathered’ by the MHRA. What this means is that all previous CAP MAs are now converted into GB national licences with Product Licence GB MA numbers, and they will be managed by the MHRA with respect to maintenance such as variations to change the terms of the MA and Pharmacovigilance activities and data. The MHRA will continue to accept the EU versions of the Risk Management Plans (RMP). For post marketing activities, the MHRA will review the EU (CHMP) assessments and opinion and if divergent opinions exist between the EU and MHRA this will be noted.

With regards to the EU, the EMA have requested that all UK sites and activities are removed from CAPs MA dossiers via variations and UK local representatives must be replaced by UK (NI) representatives who must be located in the EU or NI.

The procedures detailed in Chapter IIa of Variations Regulation (EC) No 1234/2008, which specifically applied to variations to national Marketing Authorisations, were incorporated into UK law on 31 December 2020, and continue to apply to both pending and new variations to purely national UK Marketing Authorisations. The [variations classification guideline](#), which is a fundamental component of the operation of the variations system, will continue to apply to all types of variations for all national licences.

### **3. Moving forward**

In the light of Brexit, the MHRA are taking steps to be an independent and active participant with other international regulatory authorities and the pharmaceutical industry. The measures already described are certainly designed to ensure that the UK remains a favourable environment for medical research and development. No doubt that the MHRA's new ambition, following on from Brexit, is to be a recognised leader by other international regulatory authorities and the pharmaceutical industry. The active participation in international projects, councils, organisation, and coalitions relating to the regulation of medicinal products and devices will certainly help. The MHRA are also working to encourage collaboration and co-operation by sharing of information for applications with different country members, consequently streamlining regulatory processes. These measures will help to promote the UK in its new international setting.

#### **3.1 ICH Member**

The UK is currently aligned to the ICH guidelines and the UK is to become a member of the ICH to contribute and participate in the work of the ICH. The MHRA formally applied to be an observer in February 2021, and they were admitted as an observer by the ICH Assembly at their meeting in early June 2021. The ICH Assembly adopted a new expedited procedure for membership where regulatory authorities have adopted at least 75% of the ICH guidelines. Since the UK has adopted all the ICH guidelines the aim is that the new expedited process will be applicable to the UK and ensure the admission of the UK as Member at the next ICH Assembly in November 2021.

#### **3.2 Access Consortium**

The UK MHRA is part of the Access Consortium along with the Therapeutic Goods Administration, Health Canada, Health Sciences Authority of Singapore and Swissmedic.

The consortium is a medium-sized coalition of regulatory authorities that work together to promote greater regulatory collaboration and alignment of regulatory requirements. The consortium's goal is to maximise international co-operation between partners in the consortium, reduce duplication, and increase each agency's capacity to ensure patients have timely access to high quality, safe and effective therapeutic products.

The MHRA has commenced work-sharing applications with Access partners from 1 January 2021. This information is available from the [MHRA Website](#).

#### **3.3 Project Orbis**

Project Orbis is a programme coordinated by the US Food and Drug Administration (FDA) to review and approve promising cancer treatments. It provides a framework for concurrent submission and review of oncology products among international partners. It aims to deliver faster patient access to innovative cancer treatments with potential benefits over existing therapies across the globe.

The MHRA participate fully in the scheme since 1 January 2021. While the FDA serves as the primary coordinator for application selection and review, Project Orbis Partners (POPs) may propose products for inclusion in the scheme. It involves the regulatory authorities of the following countries:

- Australia (TGA)
- Canada (Health Canada)
- United Kingdom (MHRA)
- Singapore (HSA)
- Switzerland (Swissmedic)
- Brazil (ANVISA)

Each country remains fully independent on their final regulatory decision. Applications submitted to the MHRA within a Project Orbis procedure are national (GB only) marketing authorisation applications and variations. This information is available from the [MHRA Website](#).

#### **4. Cell and Gene Therapy Catapult (CGTC)**

The current approach for CGTC on the management of the changes in regulatory areas resulting from Brexit is to continue to monitor, review, and ensure compliance with the relevant requirements for the development and manufacture of ATMPs, the conduct of clinical trials and marketing authorisation applications within the UK, the EU, and international regions.

CGTC will implement the relevant internal policies and procedures relating to both the UK and the EU and advise collaborators likewise.

With regards to Brexit, divergences between EU and UK law are being actively monitored and the impact to regulatory strategy and long-term plans will be communicated to our collaborators.

CGTC will continue to utilise the resources provided by the MHRA (such as, EAMS, ILAP, UK Combined Review process, Innovation and Scientific Advice etc.) to encourage and enable collaboration with developers to promote the UK as a country



for the medical research and development including UK patient access, to ATMPs, otherwise developed outside of the UK. CGTC are continuing the core mission to advance the growth of the United Kingdom's ATMPs industry and to enable UK to become a centre of excellence in this area during the current Brexit environment and challenge that it brings and beyond.