SIDLEY

Regulation of Human Medicinal Products

February 11, 2021

DHSC proposes creation of a publicly funded and operated medicines registries.

The DHSC has published a White Paper, 'Integration and Innovation: working together to improve health and social care for all' which sets out the DHSC's legislative proposals for a Health and Care Bill. The proposals include measures to allow the MHRA to develop and maintain publicly funded and operated medicine registries so that patients and their prescribers, as well as regulators and the NHS, can be provided with the evidence they need to make evidence-based decisions. The aim is to enable the establishment and operation of a comprehensive medicine information system, including data collection from private providers, which will support UK wide medicine registries.

January 6, 2021

MHRA updates its guidance on registering to make submissions to the MHRA from January 1, 2021

The MHRA has updated its guidance on registering to make submissions related to human medicines directly to the MHRA. The MHRA updated the section on the transition between reporting to the EU and UK system to include a list of reports received via the EMA from the December 28, 2020 to December 31, 2020. See the updated guidance here.

January 6, 2021

MHRA publishes guidance on how to tell if your product is a medicine

The MHRA has published guidance on how it makes decisions on what is a medicinal product (borderline products). See the guidance here.

December 31, 2020

MHRA publishes guidance on registering to make submissions to the MHRA

The MHRA has published guidance explaining that submissions related to human medicines need to be submitted directly to the MHRA. See the guidance here.

December 31, 2020

MHRA publishes guidance explaining how the way that you apply to licence biological products has changed from January 1, 2021

The MHRA has published guidance on licensing biosimilars, Advanced Therapy Medicinal Products and Plasma Master Files from January 1, 2021. See the guidance here.

- **New Marketing Authorisation Procedures**

March 30, 2021

There has been guidance on the **Innovative Licensing and Access Pathway** ("ILAP"), a new pathway supporting innovative approaches to the safe, timely and efficient development of medicines to improve patient access.

Please see below the main takeaways from this guidance:

Summary

- The ILAP aims to accelerate the time to market, facilitating patient access to medicines, including **new chemical entities**, **biological medicines**, **new indications** and **repurposed medicines**.
- The ILAP is open to both **commercial** and **non-commercial developers** of medicines (**UK based** and **global**), and it provides them with opportunities for enhanced regulatory and other stakeholder input.
- It comprises an **Innovation Passport** designation, a **Target Development Profile** ("TDP") and provides applicants with access to a **toolkit** (a collection of activities and assessments) to support all stages of the design, development and approvals process.

Eligibility through the Innovation Passport

- The first step in the ILAP is the **Innovation Passport application**.
- It is open to developers at the **pre-clinical trial** stage through to the **mid-development programme** point.
- The passport includes a **broad and inclusive definition of innovation** and both new and repurposed medicines are within scope.
- This designation is linked to a portfolio of activities through the creation of a **product-specific** Target Development Profile ("TDP"), only accessible through the Innovation Passport designation, which:
    - Defines key regulatory and development features, identify potential pitfalls and create a road map for delivering early patient access.
    - Includes details about how a developer can work with other UK stakeholders for coordinated and efficient evidence generation and evaluation and address commercial and managed access considerations.
    - Is expected to be a living document, updated along the development programme timelines and milestones as new knowledge is generated; therefore, for products that enter the ILAP at an early stage there will be multiple TDP versions as data are generated with the product.
    - Involves a TDP Roadmap, which provides a pathway for facilitating a regulatory and access ready approach to medicines development; the TDP Roadmap indicates the tools that are considered important for the advancement of the product through to regulatory approval and patient access and identify key areas for future engagement.
- The evidence required for a product to fulfil the criteria **can be based on non-clinical data** and depends on **where in the development pathway** the product is.
- The ILAP does not replace the Early Access to Medicines Scheme ("EAMS"), which remains an important flexibility for earlier patient access towards the end of the development programme in areas of unmet medical need and where major advantage over existing therapies can be demonstrated. The ILAP is broader in scope and is open to all innovative products. Both initiatives can be applied for.
- An Innovation Passport application is required for each separate medicinal product (different active substances); however, a single Innovation Passport can cover multiple indications for the same medicine (active substance).

Criteria

The **three** criteria for the passport are:

1. Details of the condition, patient or public health area:

- **The condition is life-threatening or seriously debilitating.**
  (*Note: for this, a summary is expected of the condition and the life threatening or seriously debilitating nature including symptoms, life span and quality of life aspects and current treatment landscape*)
  Or
- **There is a significant patient or public health need.**
  (*Note: clearly defined evidence of a specific need is required (for example, a need for paediatric formulation, anti-microbial resistance), putting the need into the context of the current patient or public health setting. This evidence is likely to be generated from information in the public domain and or patient engagement activities. For a justification of 'significant', the magnitude of the issue(s) should be discussed in a problem statement along with the identified gaps that remain in the current treatment landscape*)

Note: This is not necessarily linked to the product as it sets out the grounds for the need to develop a medicinal product in a particular area.

2. The medicinal product fulfils **one or more** of a specific area (to be indicated by the applicant):

a) Innovative medicine such as an advanced therapy medicinal product ("ATMP") or new chemical or biological entity or novel drug device combination.
b) Medicines being developed in a clinically significant new indication for an approved medicine.
c) Medicines for rare disease and / or other special populations such as neonates and children, elderly and pregnant women.
d) Development aligning with the objectives for UK public health priorities such as the Chief Medical Officer, Department of Health and Social Care ("DHSC") or Life Sciences Sector Deal, including those in Devolved Administrations, where appropriate.

Depending on the area, the following evidence must also be provided:

- A full regulatory description of the product so that the product status can be determined (e.g. name of drug substance, pharmaceutical form, route of administration, mechanism of action).
- A description of the new indication in the context of the patient group, including the novelty of the proposal.
- A description of the use of the medicine in a particular special population.
- A description of where and how the product will fulfil public health priorities.

3. The medicinal product has the potential to offer benefits to patients:

- A summary must be provided of how patients are likely to benefit from the product or indication coming to market, including proposed improved efficacy or safety, contribution to patient care or quality of life, as compared to alternative therapeutic options.
- This evidence should be based on evidence from the applicant with the product.
- The claims can be supported either by data from valid non-clinical models of the condition or if justified extrapolated from another relevant model.

- Depending on the stage of development of the product any available clinical data in a relevant population of patients can be provided.
- Applicants are strongly encouraged to include the views from patients or patient organisations around the benefits of a product in their evidence, if available.

Application for an Innovation Passport

- Applicants that wish to apply for an Innovation Passport should complete the submission form below. You will then be invited to meet with the MHRA to discuss how your product fulfils the three criteria (usually within 4-6 weeks following receipt of the application form).
- Following the meeting, the partners (MHRA, NICE and SMC) will jointly consider if the criteria have been fulfilled and you should be informed of the outcome within 4 weeks.
- To apply, fill in the Innovation Passport application form.

When to enter the pathway

- The ILAP enables multiple entry points depending on:
  - the stage of development of the product
  - the data available
  - the ambition of the applicant to engage with UK stakeholders
  - the applicant's appetite for new innovative ways of working

- The ILAP allows entry very early, based on non-clinical data, where all the tools described below might be options, as well as catering for products with mid-development 'global' dossiers.
- However, to maximise the benefits, applicants are encouraged to apply early in the development of their products.
- Products that are towards the end of their development programme are generally not suitable for the ILAP unless there are one or more indications still under active investigation.

ILAP Partners

Permanent partners in the ILAP:
- The Medicines and Healthcare products Regulatory Agency ("MHRA")
- National Institute for Health and Care Excellence ("NICE")
- Scottish Medicines Consortium ("SMC")

Supporting partners include:
- NHS England and NHS Improvement
- Health Research Authority ("HRA")
- National Institute for Health Research ("NIHR")

Fees

- **MHRA:** Innovation Passport fee: £3,624; Initial TDP fee: £4,451
- **NICE:** NICE's main contributions to the ILAP will be provided through the Office for Market Access and NICE Scientific Advice and existing fee structures will be applied.

Note: fees from other partner organisations may also apply.

Data sharing and confidentially

- Any information shared during the ILAP is considered confidential.
- It is held on a secure shared digital platform for access by the ILAP partners, as agreed by the applicant.
- In order to maximise the benefits of collaborative working with multiple UK stakeholders, the current and future sharing of relevant data is highly recommended.
- The partners adhere to relevant institutional confidentiality and non-disclosure agreements.

Contact details

- For help with the Innovation Passport: innovationpassport@mhra.gov.uk
- For queries about the Target Development Profile: TDP@mhra.gov.uk

February 1, 2021

MHRA publishes guidance on the marketing authorisation submission dates for the new 150-days national and European Commission decision reliance procedures

The MHRA has published guidance on the submission dates for the accelerated assessment and European Commission decision reliance procedures. Additionally, the guidance sets out how the submissions using the European Commission decision reliance procedure work. See the guidance here.

January 21, 2021

MHRA updates its guidance on handling of Decentralised and Mutual Recognition Procedures which are approved or pending

The MHRA has updated its guidance on the approach the MHRA intends to take for products approved or pending in decentralised or mutual recognition procedures. The update clarifies that UK national marketing authorisation applications can be submitted irrespective of applications for the same product in the EU and provides clarification of options for ongoing procedures that were not completed by December 31, 2020. See the updated guidance here.

January 4, 2021

MHRA publishes guidance on Unfettered Access Procedure for marketing authorisations approved in Northern Ireland

The MHRA has published guidance on how to apply for the Unfettered Access Procedure for marketing authorisations approved in Northern Ireland via European procedures or via the Northern Ireland National route. To be eligible, the marketing authorisation holder must be established in Northern Ireland, and the product to be placed on the market in Great Britain must be a Qualifying Northern Ireland Good. See the guidance here.

January 4, 2021

MHRA publishes guidance on the European Commission Decision Reliance Procedure

The MHRA has published guidance on how to apply for marketing authorisation the new European Commission Decision Reliance Procedure. For a period of two years from January 1, 2021, when determining an application for a Great Britain Marketing Authorisations, the MHRA may rely on a decision taken by the European Commission on the approval of a new MA in the centralised procedure. See the guidance here.

January 4, 2021

MHRA publishes guidance on the decentralised and mutual recognition reliance procedure for marketing authorisations

The MHRA has published guidance which explains how to apply for the decentralised and mutual recognition reliance procedure. See the guidance here.
January 1, 2021

MHRA announces that the new Innovative Licensing and Access Pathway is open for business

The MHRA has announced the Innovative Licensing and Access Pathway has formally started. See the press release here.

December 31, 2020

MHRA publishes guidance on 150-day assessment for national applications for medicines

The MHRA has published guidance on how the 150-day assessment timeline for all high-quality marketing authorisation applications works, and how to apply. See the guidance here.

December 31, 2020

MHRA publishes guidance on rolling review for marketing authorisation applications

The MHRA has published guidance on how the rolling review process for marketing authorisation applications will work, and how to apply. See the guidance here.

December 31, 2020

MHRA publishes guidance on the handling of applications for Centrally Authorised Products that were still pending on January 1, 2021

The MHRA has published guidance setting out how it will handle centralised applications that were still pending on January 1, 2021. See the guidance here.

December 31, 2020

MHRA publishes guidance on how it will handle decentralised and mutual recognition procedures which are approved or pending from January 1, 2021

The MHRA has published guidance which explains the approach that it intends to take for products already approved or that are included in ongoing decentralised procedures or mutual recognition procedures with the UK as a Concerned Member State and that will not be completed by December 31, 2020. See the guidance here.

December 31, 2020

MHRA publishes guidance on how marketing authorisation applications referred under Article 29 will be handled from January 1, 2021

The MHRA has published guidance on how it will assess marketing authorisation applications for medicines referred under Article 29 from January 1, 2021. See the guidance here.

December 31, 2020

MHRA publishes procedural advice for Northern Ireland on applications for European Commission Centralised Marketing Authorisations

The MHRA has issued guidance on the processes for centralised marketing authorisations granted before December 31, 2020, or submitted or ongoing from January 1, 2021 for Northern Ireland. See the guidance here.

December 22, 2020

MHRA publishes guidance on applying to the Innovative Licensing and Access Pathway for medicines

The MHRA has published guidance for applicants on applying to the Innovative Licensing and Access Pathway ('the IALP') which will be operational from January 1, 2021. The IALP aims to accelerate the time to market, facilitating patient access to medicines, including new chemical entities, biological medicines, new indications and repurposed medicines.

Guidance for New National Licensing Procedures in the UK from January 1, 2021

November 6, 2020

The Medicines and Healthcare products Regulatory Agency (MHRA) has published new **guidance** titled "Guidance note on new assessment routes from January 1, 2021." The MHRA re-issued this guidance on December 31, 2020.

Guidance on the Handling of Active Substance Master Files and Certificates of Suitability from January 1, 2021

November 3, 2020

The Medicines and Healthcare products Regulatory Agency (MHRA) has published new **guidance** titled "Handling of Active Substance Master Files and Certificates of Suitability from January 1, 2021." This guidance will apply from January 1, 2021 in line with the **Human Medicines Regulations (Amendment etc.) (EU Exit) Regulations 2019**. This guidance was re-issued by the MHRA on December 31, 2020.

From January 1, 2021, the MHRA will continue to accept Active Substance Master Files (ASMFs) and Certificates of Suitability (CEPs) in both new national initial Marketing Authorisation Applications (MAA) and in Marketing Authorisation Variation (MAV) applications.

The guidance covers the following matters:

- **Preparation of ASMF:** Should be prepared in accordance with the Committee for Medicinal Products for Human Use (CHMP) guideline on active substance master file procedure (CHMP/QWP/227/02 Rev 4)

  - Templates (letter of access; submission letter, and administrative details form) included in the annexes to that guideline should continue to be used

  - Submit the Applicant's Part (AP) of the ASMF as part of the marketing authorisation (MA) dossier, together with a letter of access issued by the ASMF holder

- **When an ASMF procedure is to be used which relates to an ASMF that has not previously been submitted to the MHRA:** The ASMF holder should submit a copy of the AP and Restricted Part (RP) to the MHRA

  - **This should be accompanied by:**

    - a completed submission letter and administrative details form;

    - any relevant letter of access;

    - the Quality Overall Summary for the AP and for the RP; and

    - a curriculum vitae for the expert

- **Submission of the complete ASMF:** The complete ASMF only needs to be submitted once to register the ASMF with the MHRA

  - Timing for the relevant documentation: Should be timed to arrive not more than one month before and not after the intended MAA/MAV submission data

- **Changes to an ASMF:** Should be handled in accordance with the CHMP guideline (CHMP/QWP/227/02 Rev 4)

  - **Responsibilities of the ASMF holder:** Notify each applicant/MA holder and the MHRA that changes are being proposed to the ASMF

  - **Submission of a new ASMF and any update to the ASMF:** Should be made by the ASMF holder using the MHRA

- **Submissions portal:** The UK will no longer participate in ASMF worksharing procedures with EU Member States

  - **Where an assessment of a new ASMF or an update to an ASMF has been conducted by an EU Member State before January 1, 2021:** Such an assessment may be taken into consideration in subsequent MAA or MAV applications that are under assessment after January 1, 2021

- **Certificates of Suitability (CEPs) are not affected by the UK leaving the EU:** They are issued by the European Directorate for the Quality of Medicines and Healthcare (EDQM) which is a Directorate of the Council of Europe and independent of the EU; on leaving the EU, the UK will remain a member of the Council of Europe

  - No change to procedures relating to the use of a CEP to support an MAA or MAV

- **Action for MA applicants:** Include appropriate information in the MAA or MAV application form

- **Applications where there is: (i) a CEP for a chemical substance that is an active substance or excipient; (ii) a CEP for a herbal drug preparation; and (iii) a CEP for materials of animal or human origin that have been subject to an evaluation of the risk related to transmissible spongiform encephalopathies (TSE):** Include a copy of the current version of the relevant CEP in Modules 1 and 3

Guidance on How and When to Register Updated Packing and Information Leaflets for Medicines When New National Marketing Authorisations (MAs) Have Been Issued from January 1, 2021

November 3, 2020

The MHRA has published new **guidance** titled "Registering new packaging information for medicines from January 1, 2021." This guidance was re-issued by the MHRA on December 31, 2020.

The guidance covers the following matters:

- **Actions to take once you have been issued a new Marketing Authorisation (MA) to convert a previously EU-wide to an MA for Great Britain:**
    - **Establish and register a Great Britain presence for your MA:** No later than 24 months from January 1, 2021
        - **Submit amended artwork for approval to accommodate the following new administrative information:**
            - Name and address of Marketing Authorisation Holder (MAH) or representative
            - Great Britain MA number
            - Name and address of product manufacturer for batch release
    - **Ensure all stock released to market is in compliant packaging:** No later than 36 months from January 1, 2021
    - **Variation application submitted between the grant of the new MA and 24 months from January 1, 2021:** You may need to amend the labelling and/or the patient information leaflet (PIL) to take account of new information; the changed artwork which accompanies that variation application should include the new administrative information at that earlier time
        - **Making changes to the labelling and/or the PIL:** Submit full colour mock-ups as part of the variation submission
        - **Only changing the name and address of the MAH and/or the manufacturer for batch release (stated in PIL):** You may do this as part of a Better Regulation of Medicines Initiative (BROMI) notification
        - **Making other changes to the statutory information or the pack design (which are not consequential to a change to the Summary of Product Characteristics (SmPC):** Submit the artwork for full assessment to the Product Information Quality Unit under change code P2

        - Normal fee arrangements apply to the above

        - **Packs containing the Falsified Medicines Directive (FMD) safety features:** Will still be accepted in the UK, provided they are in line with other UK packaging requirements

- **Multicountry packs, including packs with more than one language on the pack and/or in the PIL:** The MHRA will continue to allow these, provided that the entirety of the information is compliant with the UK requirements

- **National MAs previously the subject of a mutual recognition or decentralised submission:** Will be considered as purely national licenses

    - **Changes to packaging components which previously may have been suitable for submission via an MR 61(3) submission:** Will now be considered under the national rules

        - In many cases, these changes will be suitable for self-certification under the BROMI scheme; some changes will need to be submitted for full assessment

- See full details on how to submit applications for assessment, national best practice guidance, and the fees

Guidance on the Approach the MHRA Intends to Take to the Processing of Variations to Marketing Authorisations from January 1, 2021

November 2, 2020

The MHRA has published new **guidance** titled "Variations to Marketing Authorisations (MAs) from January 1, 2021." In line with the **Human Medicines Regulations (Amendment etc.) (EU Exit) Regulations 2019**, the Guidance will apply from January 1, 2021. This guidance was updated on December 29, 2020. The updates are particularly relevant to variations for products that were approved under mutual recognition or decentralised procedures. For approved products, marketing authorisation holders will have the option to maintain the authorisation within the mutual recognition or decentralised procedure in Northern Ireland, while maintaining a UK wide authorisation. As a consequence, importantly, variations to these marketing authorisations from January 1, 2021 may be submitted and managed as part of the relevant mutual recognition/decentralised procedure under Chapter II of Regulation (EC) No 1234/2008 with Northern Ireland as Concerned Member State, where the outcomes will be implemented UK wide. Note this when preparing and submitting any new variations from January 1, 2021 because if incorrectly submitted they will be rejected. This guidance was re-issued by the MHRA on December 31, 2020.

The Guidance covers the following matters:

- **Variations procedure for both pending and new variations to purely national UK Marketing Authorisations:** From 11 p.m. on December 31, 2020, the procedures detailed under Chapter IIa of Variations Regulation (EC) No 1234/2008 will be incorporated into UK law; can be found in new regulation 65C and Schedule 10A to the Human Medicines Regulations 2012 (HMRs)
    - **The current variations classification guidelines, which explain the type of variation (Type IA, Type IAIN, Type IB, Type II, or Extension) to submit and, where relevant,**

the conditions to be met and any required supporting documentation: will continue to apply (unless specifically highlighted below)
    - **Submission of any extension application:** submit in accordance with the procedures for new Marketing Authorisations; the variations classification guidelines will continue to apply until the MHRA issues any revised Guidance in the future
    - **Any Article 5 recommendation published by the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) before January 1, 2021:** the UK will recognise
    - **Any specific request from a Marketing Authorisation Holder (MAH) concerning the classification of a variation which is still pending (no recommendation) on January 1, 2021 or is submitted after January, 1 2021:** will need to be submitted directly to the MHRA; the MHRA will issue its own recommendation
- **Variations of a UK marketing authorisation:**
    - **All MAs authorised in the UK by the MHRA before January 1, 2021:** will be national (UK)
    - **Any pending and new variations:** will only be processed to conclusion after January 1, 2021 as national variations, where the relevant national procedures will be followed
    - **Northern Ireland:** Under the Northern Ireland protocol, medicinal products authorised via the centralised route will be directly authorised for use in Northern Ireland; a separate MA will not need to be issued by the MHRA for Northern Ireland
        - **Variations to those MAs:** will be centrally managed by the EMA in accordance with relevant procedures
        - **If the same product is separately authorised in Great Britain:** a separate variation application will need to be submitted to vary that authorisation
            - Type IA notifications: Can only be processed on the basis of what is actually submitted to the MHRA for Great Britain
            - Type IB and Type II variations: If such a variation is submitted for the corresponding Great Britain authorisation, after approval of the identical changes by the EMA, and evidence of this is included with the submission, this will be taken into consideration according to the reliance route for variations
            - A lower fee will be charged
        - **Products authorised under EU mutual recognition or decentralised (MR/DC) procedures** (See guidance concerning the handling of Decentralised and Mutual recognition procedures approved or pending)**:** Under the Northern Ireland protocol, medicinal products authorised via the MR/DC procedure, where Northern Ireland is specifically included as a concerned Member State, may be authorised for use in Northern Ireland only, where a UK MA in respect of Northern Ireland (PL(NI)) will be issued by the MHRA, or as a UK wide MA (PL) with Northern Ireland as a Concerned Member State and Great Britain aligned with the decisions taken by the Reference Member State, but not part of the DCP/MRP
            - **Variations to these MAs:** will be managed as part of the specific MR/DC procedure, according to the relevant procedures laid down in the Variations Regulation (EC/1234/2008 as amended), where worksharing will also be possible
            - **Where a UK wide MA is involved:** the MR/DC variation decision applies UK wide so it can be implemented unless the MHRA notifies the marketing authorisation holder within 30 days of the Reference

Member State decision that it cannot be accepted in Great Britain; in this case, a separate MA for Great Britain will need to be issued
        - **Where a PL(NI) is issued**: if the same product is separately authorised in Great Britain, a separate variation application will need to be submitted to vary that authorisation under domestic legislation
            - **T**ype IA notifications can only be processed on the basis of what is actually submitted to the MHRA for Great Britain.
            - For Type IB and Type II variations, if such a variation is submitted for the corresponding Great Britain authorisation, after approval of the identical changes by the Reference Member State, and evidence of this is included with the submission, this will be taken into consideration according to the reliance route for variations
            - A lower fee will be charged and there will be no fee if the Great Britain authorisation was granted under the unfettered access route, based on a purely national Northern Ireland authorisation; further guidance will be issued in due course
    - **How pending variations (no decision) on January 1, 2021 will be finalised:**
        - **Purely national Marketing Authorisations (not part of any worksharing procedure):** will be processed to conclusion under the transitional provisions, using the same purely national procedures that were in place prior to January 1, 2021
        - **UK Marketing Authorisation covered under Chapter II of Regulation (EC) No 1234/2008 (variations to marketing authorisations granted in accordance with Chapter 4 of the 2001 Directive, i.e., MR/DC variations (Type IA, Type IB, or Type II) and purely national Marketing Authorisations before 1 January 2021, but part of a worksharing procedure under Article 20 of Regulation (EC) No. 1234/2008 (Type IB or Type II):** will be processed to conclusion after January 1, 2021 as MR/DC variations using the relevant MR/DC procedures led by the Reference Member State, where Northern Ireland will be a Concerned Member State
        - **Purely National Marketing Authorisations before 1 January 2021, but part of a worksharing procedure under Article 20 of Regulation (EC) No. 1234/2008 (Type IB or Type II):** Any worksharing variation involving purely national Marketing Authorisations will be processed to conclusion after January 1, 2021 as part of the existing worksharing procedures led by the relevant Reference Authority.
            - **Action to take if the applicant does not wish to continue with the relevant variation as a national (UK) application:** notify the licensing authority in writing to say you no longer want the application to proceed; a partial fee refund may be applicable
- **Final decision for a variation procedure has been taken by the lead authority but not finally processed in the UK before January 1, 2021 where the UK is not the Reference Member State or Reference Authority:** the MHRA will implement the agreed outcome of the procedure
- **New variations submitted from January 1, 2021:** will be processed as purely national variations according to the same transposed procedures as were in place prior to January 1, 2021 or those which were already part of MR/DC procedures prior to then, which will continue to be processed as MR/DC variations

- **New variations submitted from January 1, 2021 to MAs issued as a result of Northern Ireland's involvement in European procedures:** will be managed in line with the base procedures
    - **All other new variations:** will be processed as purely national variations according to the same transposed procedures as were in place prior to January 1, 2021
    - Worksharing will only be possible for purely national Marketing Authorisation authorised for use only in Northern Ireland
        - However, provided the identical Type IB or Type II variation has already been approved for a related European Marketing Authorisation and evidence of this is included with the submission, this will be taken into consideration during the assessment process according to the reliance route procedure
    - A lower fee will be charged and there will be no fee if the Great Britain authorisation was granted under the unfettered access route, based on a purely national Northern Ireland authorisation
- **Points to note for specific changes submitted from January 1, 2021:**
    - **Change to finished product manufacturing site (including, as appropriate, primary and/or secondary packaging site):** should be submitted under the relevant sub-change code under B.II.b.1 and be suitably supported; this includes the submission of a copy of the relevant manufacturing authorisation or, as appropriate, a valid good manufacturing practice (GMP) certificate issued by the UK, or a GMP certificate (or equivalent document) from the competent authority of a country on the approved country for batch testing list (currently EEA Member States, Australia, Canada, Israel, Japan, New Zealand, Switzerland, and the United States); where relevant, reference to the EudraGMP database will suffice
    - **Change to importer/batch release site/quality control site:** should be submitted under the relevant change code under B.II.b.2 and be suitably supported
        - Importer/batch release: change should be supported by including a copy of the relevant manufacturing authorisation or a valid GMP certificate issued within the last three years (as issued by the UK or a country included on the approved country for import list (currently EU/EEA Member States)); where relevant, reference to the EudraGMP database will suffice
        - **Quality control site:** change should be supported by including a copy of the relevant manufacturing authorisation or a valid GMP certificate (as issued by the UK or a country included on the approved country for batch testing list (currently EEA Member States, Australia, Canada, Israel, Japan, New Zealand, Switzerland, and the United States); see separate Guidance considering any specific exclusions; where relevant, reference to the EudraGMP database will suffice
    - **Change of marketing authorisation holder (MAH) e.g., from a company outside the UK to one established in the UK:** cannot be done as a variation
        - Requires submission of a Change of Ownership application
        - From January 1, 2021 the MAH will have 24 months to comply with rules on establishment in the UK
        - **In the interim:** the MHRA will require a contact in the UK; the MHRA will contact EU or EEA MAHs to ask for details of a UK contact
    - **Change to the name/address of the MAH:** can be submitted as a Type IA IN under change code A.1, provided that it is not a change to the legal entity
    - **Change to the location of the Pharmacovigilance Systems Master File (PSMF) or the Qualified Person for Pharmacovigilance (QPPV):** should be submitted under

change code C.I.8.a (Type IA IN), provided the conditions and documentation requirements can be fully met
    - **The QPPV for UK authorised products:** must be established in the EU/EEA or UK on day one
    - **The PSMF for UK authorised products:** must be accessible electronically from the UK at the same site at which reports of suspected adverse reactions may be accessed
        - See separate guidance on submission of pharmacovigilance details
- **Implementation of the outcome of referrals and procedures concerning the Periodic Safety Update Report (PSUR) or post-authorisation safety studies (PASS):**
    - **Where the procedure has been finalised before January 1, 2021:** the outcomes in relation to any required variations will be processed based on the decision already taken; depending on the nature of the required changes, the variations should be submitted under the relevant main change codes of C.I.3 or B.V.b (usually type IA); the actual submission category will depend on the specific nature of the required changes, taking into consideration if further assessment is required and its level
    - **From January 1, 2021:** The MHRA will be carrying out its own assessments; the outcomes of these assessments will be published together with advice on implementation
        - Where the procedure is ongoing, the outcome of the procedure should be implemented via the appropriate route
        - Where a variation is required it will usually be a Type IA
- **Submission of protocols and final study reports for post authorisation safety studies (PASS) (although not actually variations), whether or not carried out in relation to a condition of the MA or voluntarily:** should be submitted to the MHRA within 12 months of the end of data collection; these will be processed according to the Type II variations procedure; they should be submitted under change code C.I.13
    - The submission should be accompanied by the appropriate fee, which is the same as that of a Type II or Type II complex variation
- **Submission of paediatric study reports for assessment:** From January 1, 2021 holders of a UK marketing authorisation who sponsor a paediatric study (which involves the use in the paediatric population of a medicinal product to which that authorisation relates) must submit the results of this study to the MHRA within the period of six months from the end of the study
    - **Where an initial appraisal indicates that an assessment is required:** the MAH will be asked to submit the paediatric data as a Type II complex variation to MHRA under change code C.I.13
    - **If the results of a paediatric study have been submitted for assessment to EMA or CMDh under Article 46 of Reg. 1901/2006/EC prior to January 1, 2021:** The MHRA will request MAHs to submit a Type IB variation to update the product information (PI) if there are proposed changes to the PI that can be directly implemented to relevant UK products following the completion of the EU procedure

Guidance on Renewing Marketing Authorizations for Medicines from January 1, 2021

October 30, 2020

The MHRA has published new **guidance** titled "Renewing Marketing Authorisations for medicines from 1 January 2021." This guidance was re-issued by the MHRA on December 31, 2020.

The guidance covers the following matters:

- **Renewals for Centrally Authorised Products (CAPS) converted from EU to UK Marketing Authorisations (MAs):** Treated as if they were granted on the date the corresponding EU MA was granted; the renewal date will stay the same
    - Your MAs will remain in force until a decision has been made on your renewal applications
- **Renewals submitted for MAs granted through mutual recognition or decentralised procedures:**
    - **If you do not get a decision before January 1, 2021:** You do not need to resubmit the renewal
    - **If a final decision has been made on your renewal, but it has not been processed in the UK before January 1, 2021:** The MHRA will implement the agreed outcome
    - **Where a final decision has not been made:** The MHRA will ensure that the renewal process is concluded and processed by the appropriate route
- **Renewals for MAs submitted from January 1, 2021:** Continue to submit your renewal applications nine months before they expire
    - **Requirements for renewal submissions:** Remain the same for products authorised in the UK; should include the documents currently required in the EU as detailed in the following guidance: (i) CAP renewals and annual reassessments; (ii) Renewals for products authorised through MRP or DCP procedures
        - **Reduced submission requirements:** The MHRA will continue to accept the reduced submission requirements for renewals of MAs for products authorised under Article 10.1 as set out in the CMDh Best Practice Guide on processing renewals in the MRP/DCP
- **Renewals for conditional MAs submitted from January 1, 2021:** Continue to submit your renewal applications six months before they expire
    - **Great Britain MAs and converted EU MAs that were granted as conditional MAs:** Submit the application to the MHRA
- **Renewals for MAs granted via the Unfettered Access route:**
    - **Great Britain-only MA:** Submit an application to renew the MA in line with the above guidance
    - **MA remained in line with the EU or Northern Ireland MA:** The MHRA will accept the same renewal application as submitted to the EU; a reduced fee will apply
- **Changes to fees:**
    - **First renewal of a product containing a new active ingredient at the time of authorisation:** £9,682

  - **Related applications made at the same time as the first renewal:** £747

- **No fees:**
  - **Subsequent MA renewal applications**
  - **Renewing conditional MAs**

Guidance on Great Britain Conditional Marketing Authorisations, Great Britain Marketing Authorizations under Exceptional Circumstances and National Scientific Advice from January 1, 2021

October 30, 2020

The Medicines and Healthcare products Regulatory Agency (the MHRA) has published new **guidance** titled "Conditional Marketing Authorisations, exceptional circumstances Marketing Authorisations and national scientific advice from 1 January 2021." This Guidance will apply from 1 January 2021. This guidance was re-issued by the MHRA on December 31, 2020.

The Guidance covers the following matters:

- **Great Britain conditional Marketing Authorisations (MAs):** From 1 January 2021, the MHRA will introduce a new Conditional Marketing Authorisation (CMA) scheme for new medicinal products in Great Britain; CMAs will be valid for one year and will be renewable annually
  - **Eligibility criteria of the new scheme:** the same as the EU scheme; intended for medicinal products that fulfil an unmet medical need
    - **When is eligibility determined:** at the time of the Marketing Authorisation Application (MAA) assessment
  - **Actions for those submitting a conditional MAA:**
    - **MAA must contain:** adequate evidence of safety and efficacy to enable the MHRA to conclude that the risk-benefit balance of the medicinal product is positive
    - **Applicants should:**
      - (i) state their justification for a CMA and clearly indicate what clinical studies are under way and when comprehensive clinical data will become available
        - The MHRA may grant a CMA where comprehensive clinical data is not yet complete but it is judged that such data will become available soon
      - (ii) submit their MAA dossier as for a full MA
  - **Assessment of a conditional MAA dossier:** The MHRA will determine whether to approve the application and grant a CMA or whether the risk-benefit ratio is negative and reject the application

        - The MHRA may take into account the designation of a product as being eligible for a CMA by the EMA or another jurisdiction; the final decision on eligibility for the Great Britain scheme rests with the MHRA

    - **Northern Ireland MA applications for products falling within the mandatory scope of the Centrally Authorised Procedure:** submit to the EMA

- **Great Britain MAs under exceptional circumstances:** The MHRA's existing scheme will continue to be available for medicines where a comprehensive data package cannot be provided because (i) the condition to be treated is rare, or (ii) because collection of full information is not possible or is unethical

    - **Eligibility criteria:** The scheme has the same eligibility criteria as the EU; approvals will only be granted where there are exceptional circumstances and where the applicant can demonstrate that it is not possible to provide comprehensive data on the efficacy and safety under normal conditions of use

        - The MHRA may take into account the designation of a product as being eligible for an exceptional circumstances scheme by the EMA or another jurisdiction; the final decision on eligibility for the Great Britain scheme rests with the MHRA

    - **Actions for those applying for UK MAs under exceptional circumstances:**

        - Applicants are required to discuss their submissions with the MHRA before submitting their MAA

        - The MHRA is likely to impose specific obligations on the holder of an MA that is approved under exceptional circumstances; these will be communicated to the applicant during the review and will be aimed at the provision of information on the safe and effective use of the product

    - **Applications for MAs under Exceptional Circumstances in Northern Ireland:** submit to the EMA

- **National scientific advice:** The MHRA will continue to offer its national scientific advice service, available for developers of medicinal products, and can be requested at any stage of the product's development, after 1 January 2021

    - **Fees payable for scientific advice:**

        - **Exempt from the fee:** Applications for scientific advice submitted by UK-based small and medium-sized enterprises (SMEs); applicants are required to submit evidence of their SME status together with the scientific advice form

        - **No fee:** requests for advice that is purely regulatory in nature

- **<u>Conversion of Centrally Authorised Products to UK Marketing Authorisations</u>**

Medicines and Healthcare Products Regulatory Agency Clarifies its Approach for Pending Variations to Converted EU Marketing Authorizations

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December 31, 2020

As the end of the Brexit transition period draws closer, the UK Medicines and Healthcare products Regulatory Agency (MHRA) has provided welcome clarification for the industry as to how it will deal with pending variations to converted EU marketing authorizations starting January 1, 2021. Read more **here.**

MHRA Updates its Guidance on Converted Centrally Authorised Products into UK Marketing Authorisations from January 1, 2021

November 30, 2020

The MHRA has updated its guidance on converting Centrally Authorised Products into UK Marketing Authorisations from January 1, 2021. The update helps clarify how the MHRA will approach variations that are pending at January 1, 2021 and provides further information as to how the MHRA will process new variation applications submitted to it after the end of the transition period. See the updated guidance **here.**

Guidance Setting Out How the Medicines and Healthcare Products Regulatory Agency (MHRA) Will Handle Centralised Applications That Are Still Pending on January 1, 2021

November 5, 2020

The MHRA has published new **guidance** titled "Guidance on the handling of applications for Centrally Authorised Products (CAPs) pending on January 1, 2021."

Guidance on Converting Centrally Authorised Products (CAPs) to UK Marketing Authorisations (MAs) from January 1, 2021, "Grandfathering" and Managing Lifecycle Changes

November 4, 2020

The Medicines and Healthcare products Regulatory Agency (MHRA) has published new **guidance** titled "Converting Centrally Authorised Products (CAPs) to UK Marketing Authorisations (MAs) from January 1, 2021, 'grandfathering' and managing lifecycle changes." This guidance will apply from January 1, 2021 in line with the **Human Medicines Regulations (Amendment etc.) (EU Exit) Regulations 2019**. The MHRA re-issued this guidance on December 31, 2020.

Guidance on Conversion of Community Marketing Authorisations (CAPs) to Great Britain Marketing Authorisations (MAs)

October 27, 2020

The MHRA has published new **guidance** titled "Conversion of Community Marketing Authorisations (CAPs) to Great Britain Marketing Authorisations (MAs)" to inform marketing authorisation holders of Centrally Authorised Products (CAPs) of the actions they need to take and the actions the MHRA intends to take concerning CAPs for the continued authorisation of medicinal products at the end of the transition period.

Transitional provisions in Human Medicines Regulations (Amendment etc.) (EU Exit) Regulations 2019 will ensure that all currently granted CAPs automatically become Great Britain MAs on January 1, 2021.

The guidance covers the following matters:

- **MHRA actions to facilitate the grandfathering process:** Will assign a Great Britain Product Licence (PLGB) number to CAPs based on the existing practice for national licences

- **Actions for marketing authorisation holders of a CAP:**

    - Review list of currently authorised CAPs; advise the MHRA ASAP of any errors or omissions in that list

    - Advise the MHRA of any CAPs you do not want converted into Great Britain MAs; if you are planning to opt out of having a GB licence for a product, advise the MHRA of this ASAP, ideally as part of your full return, or, if not, via a separate communication to the MHRA

        - Marketing authorisation holders can opt out of the conversion process for all or some of their CAPs by notifying us in writing by January 21, 2020

            - After January 21, 2020, the product(s) will no longer be licensed in Great Britain and can no longer be placed on the market in Great Britain

    - Advise the MHRA of the Great Britain marketing status of each of the products

    - Advise the MHRA of any products/presentations that have been withdrawn or cancelled

    - Advise the MHRA of the MAH company number

    - If possible, provide the MHRA with a single point of contact for all your products; in the case of a company group, the MHRA needs a contact for each marketing authorisation holder affiliate within that group

    - Reply with the number of PLGB numbers you require, if you are intending to do a **Change of Ownership (COA)** when you submit your baseline submission

    - Inform the MHRA of which company number prefix to use; the MHRA will allocate the PL number(s) and send you an updated list to use when submitting the baseline submission

        - Advise by writing to the MHRA at **capconversion@mhra.gov.uk**

- **Fees:** There is no fee associated with the conversion from a CAP to a Great Britain MA; the annual periodic fee will be payable for converted CAPs from April 1, 2021

- **Operation of the Sunset Clause for CAPs converted to UK MAs:** The period of three years will be restarted from the date of conversion to a Great Britain MA

- **Clinical Trials**

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MHRA publishes guidance on the registration of clinical trials for investigational medicinal products and publication of summary results

The MHRA has published guidance containing information about registration of clinical trials, publishing trial results and requirements. See the guidance here.

December 31, 2020

MHRA publishes guidance on submitting clinical trial safety reports

The MHRA has published guidance on how to submit Suspected Unexpected Serious Adverse Drug Reactions and Development Safety Update Reports. See the guidance here.

Guidance on Substantial Amendments to a Clinical Trial from January 1, 2021

October 29, 2020

The MHRA has published new **guidance** titled "Guidance on substantial amendments to a clinical trial from 1 January 2021." Further guidance will be published in relation to the Northern Ireland Protocol in due course. This guidance was re-issued by the MHRA on December 31, 2020.

The guidance covers the following matters:

Change to the trial sponsor/legal representative: This is a substantial amendment requiring submission to both the MHRA and the Research Ethics Committee (REC)

- The UK requires the sponsor or legal representative of a clinical trial to be in the UK or country on an approved-country list which initially includes EU/EEA countries
- EU law requires the sponsor or legal representative of a clinical trial to be established in the EU; if you need to update your details for an ongoing trial in the EU/EEA then the substantial amendment must be submitted to the EU/EEA competent authorities using your usual method.
- 'No amendment will need to be submitted to the MHRA in the following circumstances:' with:
    - Where the sponsor or legal representative is established in the EU/EEA
    - If the legal representative for a multi-country study is based in the UK and you are updating details via an amendment to other competent authorities
    - If the sponsor is established in the UK but a legal representative is added to cover EU/EEA sites via an amendment to other competent authorities
- **To change (add/replace) any investigational medicinal product (IMP) manufacturing, certification or importation site relevant for supply of IMP to an ongoing UK trial:** A substantial amendment will be required to be submitted to the MHRA

    - **No amendment will need to be submitted to the MHRA if:** The sponsor chooses to retain an existing IMP release site for the ongoing UK trial but includes an additional EU/EEA site for trials in the EU/EEA only

        - The IMP supply chain from a country on the approved country list, which would initially include EU/EEA countries, will allow direct supply to clinical investigator sites

    - **Action to take from January 1, 2021:**

        - **If the holder is required to be included for importation to an ongoing trial:** A substantial amendment should be submitted to the MHRA to include the details of the MIA(IMP) holder performing the "supply chain oversight" role within one year of January 1, 2021

            - For up to one year after January 1, 2021 IMPs may be supplied direct from the EU/EEA MIA(IMP) holder to the ongoing Great Britain trial site without the GB MIA (IMP) oversight process

- **Amendments to the Research Ethics Committee:** The Health Research Authority (HRA) has produced guidance on when amendments are required to be submitted for REC review

Importing Investigational Medicinal Products (Imp) for Use in a Clinical Trial From Countries on a List To Great Britain

October 22, 2020

The MHRA has published new **guidance** titled "Importing Investigational Medicinal Products (IMP) from countries on a list to Great Britain." There will be a one-year transition period from January 1, 2021 to implement this guidance. This guidance was re-issued by the MHRA on December 31, 2020.

The guidance covers the following matters:

- **Introduction:** Requirements for the supply of investigational medicinal products (IMPs) are set out in the **Medicines for Human Use (Clinical Trials) Regulations 2004**. Detailed guidance on the manufacture and import of IMPs are described in **EudraLex Volume 4** and **EudraLex Volume 10**, including guidance for the issuance of the **Qualified Person Declaration** for the importation of IMPs manufactured in third countries outside the EEA.

    - These requirements will remain in effect following January 1, 2021

    - There are no changes planned regarding import of IMPs to Great Britain from countries outside the EEA

- **Import of IMPs for use in a clinical trial from countries on an "approved country for import" list** (initially, all EU and EEA countries): The Sponsor of a UK clinical trial will require a UK Manufacturing and Import Authorisation (MIA(IMP)) holder to put in place an assurance system to check that these IMPs have been certified by a Qualified Person (QP) in a listed country, before release to the trial

    - The assurance system must be overseen by a QP; however, the IMPs would not require recertification
    - 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
        - Sponsors may perform verification of QP certification in a listed country themselves if they are the holders of a UK MIA(IMP); alternatively, they may outsource this verification to a third party who holds a UK MIA(IMP)
        - The QP named on the UK MIA(IMP) that is responsible for the verification process may be resident in the UK or a listed country
        - Manufacturing activity or importation from a non-listed country: Must be certified by a QP who is resident in the UK

- **Oversight process:** There are two routes for IMPs to be received into Great Britain from a listed country for use in UK clinical trials following QP certification by the listed country MIA(IMP) holder: (i) direct to the Great Britain clinical trial site; or (ii) via a Great Britain storage and distribution "hub"

    - **Both require the oversight of a UK MIA(IMP) holder and QP, with systems in place to ensure that:**

        - IMPs are not made available for use in Great Britain clinical trial sites until appropriate QP certification in a listed country has been verified by the QP named on the UK MIA(IMP)

        - IMPs are only shipped to appropriate Great Britain trial sites detailed within the UK trial application

        - Up-to-date information and documentation relating to the clinical trial and associated Product Specification File are made available by the Sponsor to the QP named on the UK MIA(IMP)

        - The clinical trial is authorised by the MHRA before the IMP is made available to the Investigator

    - **There should be written agreements that describe the assigned responsibilities and provision of relevant information between the organisations: These include agreements between:**

        - The Sponsor and the UK MIA(IMP) holder responsible for the oversight of import from the listed country

        - The Sponsor and the listed country MIA(IMP) holder

        - The UK MIA(IMP) holder and the Great Britain storage and distribution hub (if applicable)

        - The Sponsor and the Great Britain storage and distribution hub (if applicable)

    - **Documentation available to the QP named on the UK MIA(IMP) as part of the oversight process:**

        - Details of the manufacturing and distribution supply chain

        - The UK Clinical Trial Application form, plus amendments; this should be used to confirm the site responsible for final certification of the finished IMP

        - The UK Clinical Trial Application and any amendment approval records (including any post-approval commitment requirements)

        - Evidence that the certifying site in the listed country is appropriately licensed and holds a current GMP certificate for the IMP dosage form(s) and associated activities (e.g., manufacture, packaging, testing and/or import from a third country)

        - Details of the approved Great Britain trial sites from the ethics application, plus any updates or amendments
        - Details of each shipment of IMPs to Great Britain, including the addressees' information; this should be verified against the ethics approvals
        - Details of any excursions from the stated storage conditions during shipment, along with any decisions taken by the Sponsor and certifying QP, and the rationale for those decisions
        - Details of the responsibilities described in the written agreement between the Sponsor and the listed country MIA(IMP) holder
            - The above list is not exclusive or exhaustive; information requirements may vary depending on the responsibilities of each organisation in the supply chain
    - **Written evidence should be available to demonstrate that each batch of IMP imported from a listed country has been QP certified for use in the specified UK trial:** This should be verified prior to the first shipment of IMP from each batch to the Great Britain trial site(s); batch certification by a QP may be confirmed using evidence such as:
        - Batch certificate confirming QP certification in accordance with Article 13.3 of Directive 2001/20/EC
        - Statement of certification (ad-hoc, confirming certification in accordance with Article 13.3 of Directive 2001/20/EC)
        - Access to the certifying MIA(IMP) holder's internal systems (e.g., global Enterprise Resource Planning system) that confirms batch certification
            - Not all of the above options may be suitable for different supply chain relationships
            - Just one of the above pieces of evidence is sufficient to satisfy the requirements of the Regulations
            - Other evidence may be acceptable, provided it confirms that QP certification has taken place for the batch in question
- **Supply of IMP to a Great Britain clinical trial site:** The IMP should not be made available for use by the Great Britain clinical trial sites until the QP named on the UK MIA(IMP) confirms that the batch of IMP has been appropriately certified by the listed country QP
    - This is in addition to the two-step release procedure described in EU GMP Annex 13
    - The Sponsor should ensure that the regulatory release is in place for the UK prior to IMP being made available for use in the trial
- **Using a Great Britain storage and distribution "hub":** You may use a distribution facility to store IMPs imported from a listed country before supplying to Great Britain clinical trial sites

  - If IMPs are segregated electronically or physically until certification has been confirmed by the QP named on the UK MIA(IMP), IMPs may be imported to the distribution hub from a listed country before confirming that QP certification has taken place in the listed country

  - Great Britain storage and distribution facilities should be named on the UK MIA(IMP) of the company responsible for oversight of the import

- **Reference and retention samples:** Additional reference and retention samples are not specifically required to be stored within Great Britain

  - The storage location should be visible to the QP named on the UK MIA(IMP) and defined in the written agreement with the Sponsor

  - The relevant written agreements should include provision for timely access to the samples by the competent UK authority

- **IMPs coming to Great Britain from Northern Ireland:** Do not require this additional oversight

- **IMPs coming directly to Great Britain from third countries that are not on the approved country for import list:** Continue to require import and QP certification in the UK by the MIA(IMP) holder per the existing requirements

- **Importing non-investigational medicinal products for use in a clinical trial:**

  - **Importing from a listed country authorised or unauthorised products for use in a UK clinical trial in Great Britain that are (i) non-investigational medicinal products or (ii) unmodified comparators to be labelled in Great Britain prior to QP certification and release to the clinical trial:** Use a wholesale dealer's licence

    - A Responsible Person (import) may be required

  - **Importing from a country that is not a listed country:** Requires a manufacturer's licence

  - **Importing from Northern Ireland:** Will require a wholesale dealer's licence, unless you are the Sponsor of the clinical trial

- **<u>Pharmacovigilance</u>**

MHRA updates its guidance on pharmacovigilance procedures

The MHRA has updated its guidance summarising its approach to pharmacovigilance. See the updated guidance here.

December 31, 2020

MHRA publishes guidance on Marketing Authorisation Holder and Qualified Person for Pharmacovigilance location

The MHRA has published guidance explaining the location requirements for a Marketing Authorisation Holder and a Qualified Person responsible for Pharmacovigilance.

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December 31, 2020

MHRA publishes guidance on the exceptions and modifications to the EU guidance on good pharmacovigilance practices that will apply to UK marketing authorisation holders and the MHRA

The MHRA has published guidance which clarifies the expectations on the application of the EU guidance on good pharmacovigilance practices. See the guidance here.

November 30, 2020

MHRA Updates its Guidance on Pharmacovigilance Procedures from January 1, 2021

The MHRA has updated its guidance on pharmacovigilance procedures from January 1, 2021. The update relates to the country codes and worldwide case IDs that should be used when submitting Individual Case Safety Reports (ICSRs). See the updated guidance **here.** The MHRA re-issued this guidance on December 31, 2020.

Guidance for Marketing Authorisation Holders for Medicines Authorised in Great Britain on the Submission Requirements for Pharmacovigilance Data from January 1, 2021

November 6, 2020

The MHRA has published new **guidance** titled "Updated guidance on pharmacovigilance procedures." From January 1, 2021, the MHRA will retain responsibility for pharmacovigilance across the UK. There will be some different requirements for products placed on the market in the UK with respect to Great Britain and Northern Ireland. For products placed on the market in Northern Ireland requirements will, in general, remain in line with EU requirements.

Guidance on Pharmacovigilance System Requirements Applying to Holders of UK Marketing Authorisations from January 1, 2021

October 29, 2020

The MHRA has published new **guidance** titled "Guidance on qualified person responsible for pharmacovigilance (QPPV) including pharmacovigilance system master files (PSMF) from January 1, 2021." This guidance was re-issued by the MHRA on December 31, 2020.

The guidance covers the following matters:

- **From January 1, 2021 the following legal obligations will apply to holders of UK marketing authorisations (MA)** (including those that over the whole of the UK, or are specific to Northern Ireland or to Great Britain, including Great Britain MAs granted to allow unfettered access from Northern Ireland):
    - **To operate a pharmacovigilance system for UK-authorised products**
    - To have permanently and continually at its disposal an **appropriately qualified person responsible for pharmacovigilance (QPPV)** that resides and operates in the EU or the UK and is responsible for the establishment and maintenance of the pharmacovigilance system for UK-authorised products

- **QPPV is not in the UK:** You must nominate a national contact person for pharmacovigilance who resides and operates in the UK and reports to the QPPV
    - This individual should have access to the reports of suspected adverse reactions
    - The individual should be able to facilitate responses to pharmacovigilance queries raised by the MHRA, including via inspections
- **Time period for appointing a national contact person for pharmacovigilance:** 12 months from January 1, 2021
    - Once appointed: Notify their details to the MHRA via the MHRA Submissions Portal

- To maintain and make available upon request a **pharmacovigilance system master file (PSMF)** that describes the pharmacovigilance system for UK-authorised products
    - **Location and accessibility of PSMF:**
        - MAs that cover the whole of the UK or are specific to Northern Ireland: At the site in the EU where the main pharmacovigilance activities are performed or at the site where the QPPV operates; the PSMF must be accessible electronically from the UK at the same site at which reports of suspected adverse reaction may be accessed
        - **MAs that are specific to Great Britain:** The PSMF must be accessible electronically at the same point in the UK from which the reports of suspected adverse reactions may be accessed
        - The PSMF needs to be permanently and immediately available for inspection at the stated location in the UK
    - **PSMF format, content and representation of pharmacovigilance systems:**
        - A single PSMF can be used for all UK-authorised products (assuming that the pharmacovigilance system applied to all products is the same)
        - The PSMF must describe the global pharmacovigilance system and reflect the global availability of safety information for UK-authorised products
        - There are different approaches to establishing a pharmacovigilance system, e.g., (i) MAHs can establish more than one pharmacovigilance system; (ii) a pharmacovigilance system can be shared by several MAHs
        - The PSMF should be an accurate representation of the pharmacovigilance system that has been established and you must make sure that every pharmacovigilance system covering UK-

authorised products has been assigned a unique PSMF number by the MHRA

- **How to request a UK PSMF number:** All PSMFs that cover UK-authorised products should be registered with the MHRA; you should request a unique UK PSMF number from the MHRA for each pharmacovigilance system that you are operating for UK-authorised products; where the pharmacovigilance system is shared by several MAHs, a single request for a UK PSMF number should be submitted to the MHRA
    - A UK PSMF number can be requested via the MHRA Submissions Portal from January 1, 2021
    - When to request the UK PSMF number? Not until you are either applying for a new UK MA, or notifying the MHRA of a change in the details of the QPPV for UK-authorised products from the QPPV details that were registered in the eXtended EudraVigilance Medicinal Product Dictionary (XEVMPD) on December 31, 2020

- **Notification of QPPV and PSMF details to the MHRA by existing holders of UK MAs:** Submit Type IAIN variations related to the SPS to the MHRA and these submissions should cover all UK product licences (PL) under a unique pharmacovigilance system
    - **How to make your submission to update the summary of the applicant's pharmacovigilance system (SPS)?** Via the MHRA Submissions Portal as a Type IAIN – C.I.8 variation via the MHRA Submissions Portal; use Agency Activity Reference ID: G0098 – Variation Type IA – Establishing UK QPPV-PSMF and Subactivity Text: H002 – "Original Submission"
        - Submit your SPS updates as single changes
        - Submit in collections of no more than 25 PLs
        - Submit no more than two collections in a single package or within a single week without prior notification
    - **Documentation you must supply:**
        - proof that the applicant has at their disposal a qualified person responsible for pharmacovigilance and a statement signed by the applicant to the effect that the applicant has the necessary means to fulfil the tasks and responsibilities listed in Part 11;
        - the country (which must be either the UK or a Member State) in which the appropriately qualified person resides and carries out their tasks;
        - contact details of the appropriately qualified person who resides and operates in the EU or the UK;
        - a reference to the location where the PSMF for the medicinal product can be accessed, which must be in the UK;
        - the UK PSMF number

        - Failure to supply all of the above may lead to the rejection of the submission

- **Submission time frames from January 1, 2021:** Please refer to the Submission timeframe overview which has an overview of the timeframes for submitting SPS details to the MHRA

    - From January 1, 2021 you must notify the MHRA of the details in the SPS following any changes to the QPPV responsible for UK-authorised products from the baseline information held by the MHRA (i.e. the QPPV details that were registered in eXtended EudraVigilance Medicinal Product Dictionary (XEVMPD) at the end of December 13, 2020)

        - QPPV updates submitted prior to December 13, 2020: You should have received a successful acknowledgement message (coded as '01') indicating that the information in the XEVPRM has been processed successfully

        - Changes to the QPPV submitted after December 13, 2020: Will not be included in the baseline dataset

        - The submission of SPS details for licences that were authorised via the EU centralised procedure should be handled differently to UK national licences

- **Guidance relating to UK national licences (including those authorised via mutual recognition or decentralised procedures):** From January 1, 2021 if the identity, location and contact details of the QPPV responsible for UK-authorised products are identical to that of the EU/EEA QPPV immediately prior to 1 January 2021 (as entered in XEVMPD), no immediate action is required to notify the MHRA

    - **Within two weeks of a change of identity, location or contact details of the QPPV responsible for UK-authorised products:** Submit single change Type IAIN - C.I.8 variation; this should cover all UK PLs under a unique pharmacovigilance system (in collections of no more than 25 PLs)

    - **If you anticipate no changes to the QPPV details from those entered in XEVMPD by June 30, 2022:** Submit these details for the QPPV, together with the UK location that the PSMF can be accessed from and UK PSMF number as a single change Type IAIN – C.I.8 variation by this deadline

- **Licences authorised via the EU centralised procedure:** All existing MAs authorised through the centrally authorised procedure will automatically be converted into UK MAs; these MAs will be issued with a UK MA number before the end of the transition period

    - **Period to submit the baseline initiating sequence data and related information in eCTD format:** One year, starting on January 1, 2021

    - **Follow the following guidance at the point of submission of the baseline initiating eCTD sequence:**

- **Identity, location or contact details of the QPPV responsible for UK-authorised products are different to that of the EU/EEA QPPV immediately prior to January 1, 2021 (as entered in XEVMPD):** Simultaneously submit a Type IAIN – C.I.8 variation as a separate sequence in the same submission package; this variation will be processed once the baseline sequence is processed

- **Identity, location or contact details of the QPPV responsible for UK-authorised products are identical to that of the EU/EEA QPPV immediately prior to January 1, 2021 (as entered in XEVMPD):** No immediate action is required to notify the MHRA; take the following actions following receipt of the baseline sequence approval letter from the MHRA:

    - Within two weeks of a change of identity, location or contact details of the QPPV responsible for UK-authorised products: Submit a single change Type IAIN – C.I.8 variation; this should cover all UK (ex-EU) PLs under a unique pharmacovigilance system (in collections of no more than 25 PLs)

    - If you anticipate no changes to the QPPV details from those entered on XEVMPD by June 30, 2022: The details of the QPPV and PSMF should be submitted by this deadline

- **Guidance for applicants for UK MAs from January 1, 2021**

- **The material to accompany an application for a UK MA must include a summary of the applicant's pharmacovigilance system which must include the following elements:**

    - proof that the applicant has at their disposal an appropriately qualified person responsible for pharmacovigilance who resides and operates in the EU or the UK;

    - the country (which must be either the UK or a Member State) in which the appropriately qualified person resides and carries out his or her tasks;

    - the contact details of the appropriately qualified person;

    - a statement signed by the applicant which says that they have the necessary means to fulfil the tasks and responsibilities listed in Part 11;

    - a reference to the location where the pharmacovigilance system master file for the medicinal product can be accessed electronically, which must be in the UK;

    - the UK PSMF number

- **MHRA Submissions Portal:** Use Agency Activity Reference ID: G0001 – Initial Marketing Authorisation Application and Subactivity Text: H002 – "Original Submission"

    - Information on the QPPV and PSMF for UK-authorised products should be entered in section 2.4.4 of the electronic application form (eAF)

  - QPPV resides and operates in the UK: The checkbox entitled "The above-mentioned qualified person resides and operates in the EEA" can remain unchecked

  - The UK location where the PSMF can be accessed from does not need to be registered in the Article 57 database, therefore the associated checkbox can remain unchecked

- **Notification of QPPV and PSMF details to XEVMPD:**

  - **Prior to January 1, 2021:** Continue to submit QPPV and PSMF details for all UK-authorised products to XEVMPD, including any changes to these details

  - **From January 1, 2021 for products in respect of Northern Ireland (UK-wide and Northern Ireland-only MAs:** In addition to notifying the QPPV and PSMF details to the MHRA, you must also continue to submit this information to the Article 57 database.

Guidance on How to Apply to Be a Responsible Person (Import) (RPi), How to Verify That QP Certification of a Medicine Has Been Done in the EEA, and How to Verify That Biological Products (Vaccines and Medicines Derived From Human Blood or Plasma) Have an Independent Batch Release Certificate

October 22, 2020

On December 31, 2020 the MHRA re-issued its guidance titled 'Acting as a Responsible Person (import)'.

A wholesale dealer in Great Britain may only import Qualified Person (QP) certified medicines from the European Economic Area (EEA) if certain checks are made by the "Responsible Person (import) (RPi)." Great Britain is England, Wales, and Scotland.

- Section titled 'Products imported for parallel import or special need:' should begin 'From January 1, 2022 the RPi should…' and 2nd bullet point in this section should start 'From January 1, 2022 products that are supplied as decommissioned…'

- **Products that do not require RPi oversight:**

  - Products sourced from Northern Ireland for wholesale purposes; permitted under the supervision of a Responsible Person (RP)

  - Products with a UK or Great Britain marketing authorisation that are imported into Great Britain from outside the UK without QP certification from a country on the list will require QP certification under a UK manufacturing and import authorisation before being placed on the market

  - Products without a marketing authorisation in the UK, Northern Ireland, Great Britain, or a listed country; import of such products is permitted under the supervision of a Responsible Person (RP), with notification to the MHRA of each importation that is for supply to the Great Britain market

- **Responsibilities of the RPi:**

- To implement a system to confirm for products that have been imported into Great Britain from countries on an approved country for import list (initially, this will be countries in the EEA) (i) that the required QP certification has taken place; and (ii) that the required independent batch release certificate is available for biological products (described on a wholesale dealer's licence as "immunologicals and blood products")
    - The RPi may delegate this responsibility but remains responsible for ensuring the effectiveness of these checks
- To implement a system for confirming QP certification and independent batch release certification (for biological products) has taken place when importing into Great Britain the following products from a listed country:
    - A UK or Great Britain licensed medicine for use in Great Britain
    - A UK or Great Britain licensed medicine for supply to another third country
    - A Northern Ireland or approved country licensed medicine for supply to fulfil special clinical needs
    - A Northern Ireland or approved country licensed medicine imported as an introduced medicine for supply to another third country
    - A Northern Ireland or approved country licensed medicine for use as a parallel import

- **What evidence can be used for QP certification?** The RPi should ensure that written evidence is available to demonstrate that each batch of product has been QP certified as required in Article 51 of Directive 2001/83/EC
    - **Evidence for Great Britain Wholesale Dealer's Licence (WDA(H)) holders importing a UK, Northern Ireland, Great Britain, or EEA licensed medicine from a listed country to confirm batch certification by a QP:**
        - Batch certificate confirming QP certification in accordance with Article 51 of Directive 2001/83/EC
        - A copy of the "control report" (Appendix II to EU Good Manufacturing Practice Annex 16)
        - Statement of certification (ad-hoc, confirming certification in accordance with Article 51 of Directive 2001/83/EC)
        - Reference to company internal systems (e.g., global enterprise resource planning system) that shows batch certification
        - Confirmation that the final manufacturing step (other than batch certification) of an authorised medicine has been performed by a Manufacturing and Import Authorisation holder in a listed country; a copy of the Marketing Authorisation and technical agreement with the manufacturer should be available to place reliance on this supply chain control

        - For medicines authorised in a listed country, batch certification may be verified by confirming that the medicine has been purchased from an authorised wholesaler after it has been "placed on the market" in the listed country

            - Not all of the above options may be suitable for different supply chain relationships

            - Just one of the above pieces of evidence is sufficient to satisfy the requirements of regulation 45AA of the Human Medicines Regulations 2012

        - Other evidence may be acceptable if it confirms that QP certification has taken place for the batch in question

- **What evidence can be used for independent batch release certification?**

    - A statement from the marketing authorisation holder confirming that a batch certificate has been issued by NIBSC or a Mutual Recognition Agreement partner

    - A copy of the batch certificate issued by NIBSC or a Mutual Recognition Agreement partner

    - Confirmation from NIBSC that a batch certificate has been issued; enquiries should be sent to CPB@nibsc.org

        - Biological products requiring independent batch release certification are listed on the European Directorate for the Quality of Medicines website

- **Supply chain security:**

    - Checks on products imported from a listed country should also ensure that the product is not the subject of a recall or reported as stolen and is available on the market within the listed country's licensed supply chain; Good Distribution Practice (GDP) requirements for supplier qualification set out in GDP 5.2 must be maintained

    - Products that have been certified by a QP but have been diverted to countries not within a listed country or Northern Ireland must be imported by the holder of an MIA and recertified by a QP

- **Products imported for parallel import or special need:** The RPi should implement a process to confirm the status of the unique identifier for prescription-only medicines, if wholesale dealers are importing products (i) for parallel import or (ii) for use for special clinical need or introduction

    - Confirmation of decommissioning may be provided by using evidence such as National Medicines Verification System records from the supplier

    - Products that are supplied as decommissioned must be decommissioned by the final EEA supplier and not at any other point in the supply chain

- **Great Britain WDA(H) holders acting as or on behalf of the UK or Great Britain MAH:** The expectation is that products have been certified prior to importation; shipment to Great

Britain under pre-certification quarantine is not acceptable for the WDA(H) importation model

  - If supply chains require shipment under quarantine prior to QP certification for technical reasons (e.g., products with very short shelf life), the MAH should seek further advice from MHRA by email to GDP.Inspectorate@mhra.gov.uk

- **Working as an RPi:**

  - Ensure you have training and an understanding of the industry where you have the legal responsibility to ensure that batches of authorised medicines imported from countries on a list have been appropriately certified prior to being placed on the Great Britain market

  - You take responsibility for implementing a system for the WDA(H) as a whole

  - You do not have to be an employee of the licence holder; where you are not an employee, there should be a written contract between the licence holder and the RPi specifying responsibilities, duties, authority, and time on site; if you are a contract RPi, then you are expected to ensure you do not over-extend yourself and apply to act as RPi for too many companies

  - You must be continuously contactable

- **Stages to becoming named as an RPi:**

  - **Stage 1: Eligibility**

    - **Qualifications:** Diploma, certificate, or other evidence of formal qualifications awarded on completion of a university or other higher education course of study in pharmacy, chemistry, medicine, biology, or a related life science; equivalent qualifications for RPi candidates include level 5 qualifications from the Chartered Institute of Logistics and Transport, or a Quality Management System Lead Auditor or Pharmaceutical GMP Lead Auditor qualification awarded by the Chartered Quality Institute; other qualifications may be acceptable

    - **Experience:** Two years' experience in performing the functions of a responsible person on a WDA(H); evidence of performing other functions, e.g., a quality assurance role for a pharmaceutical manufacturer, may also be considered equivalent

    - It is expected that you will be a **member of a professional body** with a published code of conduct

      - Acceptable professional body memberships: The Royal Society of Biology, the Royal Pharmaceutical Society, the Pharmaceutical Society of Northern Ireland, and the Royal Society of Chemistry

      - Additional bodies considered to be equivalent: The Chartered Institute of Logistics and Transport and the Chartered Quality Institute; other professional associations may be acceptable

        - **Persons named on the Qualified Persons register will also be eligible to act as an RPi:** You must still apply to be named on the RPi register; as an alternative to providing evidence of your qualifications and membership of a professional body, you may provide evidence of your QP registration

    - Once eligibility has been assessed and accepted by MHRA, you can be named on a register; the register will be maintained by MHRA and will include all persons eligible to be named as an RPi

    - **Stage 2: Suitability** to be named on a specific WDA(H) licence

        - At the time of application, MHRA will confirm whether you are named on the register, and check whether your experience is suitable for the proposed licence activity

            - E.g., an eligible RPi without prior experience in parallel importation might not be considered suitable to be named on WDA(H) where the company are importing licensed products for parallel trade

- **Applying to be named as an RPi:** RPi applications may be submitted through the MHRA Portal from January 1, 2021

    - The RPi should be a UK resident; provide proof of address and identity when you apply

Explaining the Detailed Description of Pharmacovigilance System and Qualified Person for Pharmacovigilance (QPPV) From January 1, 2021 for the Veterinary Pharmaceutical Industry

The Veterinary Medicines Directorate (VMD) has published new guidance titled "From January 1, 2021 Pharmacovigilance System and Qualified Person for Pharmacovigilance explainer."

The new guidance covers the following matters:

- **Location of the Qualified Person for Pharmacovigilance (QPPV):**
    - **Centrally authorised Marketing Authorisations (MAs):** The QPPV must be located in the EU for these products to be on the Northern Ireland (NI) market. From January 1, 2021, for existing centralised MAs, you will be offered a GB MA for these products.
    - **GB MAs:** The QPPV can be located anywhere.
    - **MAs issued following mutual recognition/decentralised procedures:** These will continue to be issued by the VMD in respect of NI. The QPPV can be located in the EU, NI or GB, due to interpretation of the requirements of the Northern Ireland Protocol.
    - **UK national MAs (existing) and NI MAs:** The QPPV can be located in the EU, NI or GB for authorisations issued by the UK in respect of NI due to interpretation of the requirements of the Northern Ireland Protocol. The QPPV for GB MAs can be located anywhere.
- **Pharmacovigilance inspections:** From the January 1, 2021, the VMD will carry out inspections of all marketing authorisation holders (MAHs) for products authorised in the UK; this includes those MAHs located outside the UK
    - The VMD will use a risk-based approach to scheduling inspections; risk basis considerations will include last EU inspection date, previous inspection findings, and surveillance intelligence.
    - Inspections will be conducted remotely where possible.

- **Detailed Description of Pharmacovigilance system:** The UK requirement for the Detailed Description of Pharmacovigilance System is under review; the VMD will provide more information as it becomes available.

- **Paediatric Medicinal Products**

Guidance on Submission, Processing, and Assessment of All Completed Paediatric Studies Sponsored by Marketing Authorisation Holders (MAHs) from January 1, 2021

November 3, 2020

The Medicines and Healthcare products Regulatory Agency (MHRA) has published new **guidance** titled "Completed Paediatric Studies - submission, processing and assessment from January 1, 2021." This guidance was re-issued by the MHRA on December 31, 2020.

The holders of a UK marketing authorisation (MA) who sponsor a study which involves use in the paediatric population in respect of the medicinal product to which that authorisation relates must submit to the MHRA results of the study within the period of six months beginning with the day on which the trial ended; this applies irrespective of whether or not the studies are conducted in accordance with an agreed paediatric investigation plan (PIP), or the MAH intends to apply for a marketing authorisation for a paediatric indication in relation to the product. This is required by **Regulation 78A(13) and (14) of the Human Medicines Regulations 2012, as inserted by the Human Medicines (Amendment etc.) (EU Exit) Regulations 2019** which replaces Article 46 of Regulation (EC) No 1901/2006. The MHRA will also consider the outcome of Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) paediatric worksharing procedures (PdWS) reviewed under Article 45 of Regulation (EC) No 1901/2006 (as amended). If required, the MHRA will request updates to the product information (PI) for UK MAs.

The guidance covers the following matters:

- **Submission of a cover letter of the concerned paediatric study(ies) to the MHRA:** The MAH must do this within six months of completion (i.e., date of last visit of last subject undergoing the trial, unless otherwise justified in the protocol) in electronic Common Technical Document (eCTD) format via email to **paediatricstudies@mhra.gov.uk**
    - **The MAH should indicate in the cover letter whether the study(ies):**
        - **are linked to other paediatric studies which have been or will be the subject of other submissions under Regulation 78A of the Human Medicines Regulations 2012, as inserted by the Human Medicines (Amendment etc.) (EU Exit) Regulations 2019:** The MAH should provide the study title(s) with approximate date of completion; if the study(ies) relate to a UK-PIP, the MAH should provide the PIP number
        - **have been or will be submitted in the UK as part of a variation/extension or any other application including this paediatric study:** The MAH should (i) specify the UK procedure number, if available, or the type of application this will be submitted under; (ii) confirm that the application will be submitted within the next six months; and (iii) confirm that, based on the results of the study, no urgent safety update of the product information is required

- The MAH should provide any relevant information about any related Article 46 of Regulation (EC) No 1901/2006 procedure(s) or EU agreed PIP(s)

- The MAHs should also state whether as a result of the paediatric study there is a need to update the product information

- **Initial appraisal of whether an assessment procedure is required at this stage:** Carried out by the MHRA on receipt of the cover letter; one of the following may apply:

  - **Assessment of the data is not required at this stage and the MHRA will maintain records including justification for the decision**

- **Limited evaluation of the study data may be undertaken if the MAH provides robust justification that the study data are unlikely to warrant PI changes**

  - **The MAH will need to state in the cover letter that one or more of the following criteria are met:**

    - the same data have been reviewed in another regulatory procedure by the MHRA or another competent authority and the review has not led to PI changes;

    - the study was conducted mainly in adult patients with limited paediatric patients included;

    - the drug is already licensed in the paediatric population and the study does not provide new pharmacokinetic (PK), efficacy, or safety data;

    - the study, due to its design, limited number of paediatric patients, discontinuation, or other reason does not allow drawing conclusions on efficacy or safety that would impact the drug's benefit:risk ratio or be useful to prescribers and patients;

    - only interim results from an ongoing study are available which will be assessed later in their totality;

    - the study has been conducted in populations and/or diseases that are not applicable to the UK; and/or

    - other justification as to why a detailed assessment is not required at this stage

      - **One or more of the above criteria apply:** The MAH should submit the study report and a short clinical overview including justification why PI changes are not necessary; a variation application will not be requested if the MHRA agrees with the MAH's justification not to update the PI

        - **Short clinical overview to clarify the context of the data:** Should include information on the pharmaceutical formulation used in the study, the existence of a suitable paediatric formulation, and, if relevant, conditions for an extemporaneous formulation

- **If review of the data is required (when the MAH proposes a PI update or when the MHRA concludes after the initial appraisal, that a full assessment is needed to robustly conclude on prospective PI updates):** The MHRA will notify the MAH to submit the paediatric data within 60 days as a type II variation application (change code C.I.13 — complex type II variations fees will be applicable)
    - **The MAH should submit the following:**
        - Final clinical study report;
        - A short clinical overview clarifying the context of the data;
        - A summary of Product Characteristics/Patient Leaflet (SmPC/PL) proposal to update the paediatric information, or when none is considered required, justification that changes are not necessary;
        - For a paediatric study that is part of a development program including a PIP, a line listing of all relevant studies; and
        - If the MAH holds other paediatric studies for the same active substance falling under the scope of EU Article 45 of Regulation (EC) No 1901/2006 which have not yet been assessed by a competent authority, these should be submitted along with a clinical overview clarifying the context of the data
    - **If the MAH is unable to submit the type II variation within the 60-day timeframe:** The MAH must justify the delay and propose a new submission date
- **Results of a paediatric study submitted to the European Medicines Agency (EMA) or CMDh under Article 46 of Regulation (EC) 1901/2006 prior to January 1, 2021:** The process will remain within the EU assessment framework and no UK equivalent procedure will be initiated unless the MAH indicates that an urgent safety update of the PI is required
    - **Upon finalisation of the EU procedure and availability of the final assessment report:** The MAH should submit this to paediatricstudies@mhra.gov.uk
        - The MHRA will check the applicability of the outcome of the EU procedure for UK products
        - **If there are proposed changes to the PI which can be directly implemented to relevant UK products, if not already submitted:** The MHRA will request MAHs to submit a type IB variation to update the PI within 60 days
- **Workflow steps for submission and assessment of MAH-sponsored paediatric studies:**
    - **Step 1; Day 0:** Receipt of letter notifying the MHRA of completed study from MAH via paediatricstudies@mhra.gov.uk
    - **Step 2; Day 7:** Allocate procedure to medical assessor
    - **Step 3; Day 14: Inform MAH whether assessment of the data is required**
        - **If required:** A variation is requested within 60 days, go to step 4

        - **If an EMA P46 or CMDh PdWS under Article 46 of Reg.1901/2006 has been completed prior to January 1, 2021 and PI changes is a direct implementation to relevant UK products:** Go to step 11

        - **If not required:** MAH will be informed that no further action is needed

    - **Step 4; Day -14:** MAH submits data as variation type II, followed by validation process (up to 14 calendar days)

    - **Step 5; Day 0 (clock starts):** Provide MAH with the start date of the procedure

    - **Step 6; Day 59/60 (standard) (in exceptional circumstances (extended) day 89/90):** Preliminary AR followed by clock-stop period if there is a need for Request for Information (RFI) or Preliminary/Final AR, where changes to the PI could be implemented at the end of the procedure if applicable

    - **Step 7; clock-stop:** Should not be longer than 60 days for responses + 60 days for assessment of the responses (extension of clock-stop period could be considered upon request)

    - **Step 8; Day 60 (standard) (Day 90 (extended)):** Final AR sent to MAH, where changes to the PI could be implemented at the end of the procedure, if applicable

    - **Step 9; Day 75 (standard) (Day 105 (extended)):** Draft Public paediatric AR sent to MAH to comment on any confidential/commercial sensitive information within 15 days

    - **Step 10; Day 90 (standard) (Day 120 (extended)):** Publish public paediatric AR on the MHRA website

    - **Step 11; Day 60 (only applicable if an EMA P46 or CMDh PdWS under Article 46 of Reg.1901/2006 has been completed prior to January 1, 2021 and PI changes is a direct implementation to relevant UK products):** Request will be sent to MAHs for type IB variations submission, to update the PI within 60 days

- **Processing and assessment of outcome of EU Article 45 worksharing procedures:**

    - MAHs are not required to submit to the MHRA information on paediatric studies completed by January 26, 2007 and which fall under the remit of Article 45 of Regulation (EC) No 1901/2006 worksharing procedure

    - The MHRA will monitor the published Public Assessment Reports (PAR) of Article 45 PdWS procedures

        - **If a new PAR is identified:** Any proposed (PI) changes and their applicability for UK products with the same active substance will be reviewed

            - **If products with the same active substance are not available in the UK or the PI changes proposed are not applicable to UK products:** No further action will be taken

- **If the proposed PI changes are directly applicable to UK products, if not already submitted:** The MHRA will send a request to the UK MAHs to submit a type IB variation within 60 days

- **If proposed PI changes are not directly applicable to the UK products:** The MHRA may adapt the recommendations and subsequently send requests to UK MAHs for type IB variation, where the UK adapted recommendations will be provided, within 60 days

- **If the MHRA considers that the MAHs should provide supplementary data in order to conclude on potential PI changes for the UK products and a further UK assessment is deemed necessary:** A type II variation could be requested within 60 days

Guidance on the Process for Applicants Applying for a Paediatric Investigation Plan (PIP), Submitting a PIP Modification and Requesting a Paediatric Class Waiver from January 1, 2021

November 3, 2020

The MHRA has published new **guidance** titled "Procedures for UK Paediatric Investigation Plan (PIPs) from January 1, 2021." This guidance will apply from January 1, 2021 in line with the **Human Medicines Regulations (Amendment etc.) (EU Exit) Regulations 2019**. This guidance was re-issued by the MHRA on December 31, 2020.

The legal requirements for UK-PIPs are set out in the Human Medicines Regulations 2012, as amended by the **Human Medicines Regulations (Amendment etc.) (EU Exit) Regulations 2019** (HMRs), including transitional provisions.

The guidance covers the following matters:

General approach to UK-PIPs

- **The PIP application process:** The MHRA will simplify this by offering an expedited assessment (where possible) and by mirroring the submission format and terminology of the EU-PIP system

    - Scientific content and assessment required: Kept in line with EMA guidance documents

- **Northern Ireland:** Remains part of the EU's system for paediatric medicines development including agreement of EU-PIPs or waivers

- **Paediatric obligations in line with the unfettered access Great Britain Marketing Applications:** Will be met by the agreed EU-PIP or waiver as required

- **Format and submission procedure for UK-PIP applications:** Will be published separately

    - 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 in the UK

- For any UK paediatric submissions that do not fall into any of the prespecified criteria listed above: A case-by-case discussion should always be considered

- Further step-by-step information on the process of submitting PIPs via the new MHRA submissions portal will be available in a user reference guide which will be published separately

PIP submissions

EU-PIP or modifications to PIPs submitted before January 1, 2021:

- **EU-PIPs and modifications agreed by the EMA before January 1, 2021:** Adopted as UK-PIPs on or after that date; will not require resubmission to the MHRA

- **Valid request for an EU-PIP or modification or waiver made to the EMA but no decision given before January 1, 2021, and EMA Paediatric Committee (PDCO) has given a positive opinion with which the UK has concurred:** Adopted as a UK-PIP; will not require resubmission to the MHRA

- **Valid request for an EU-PIP or modification or waiver made to the EMA, but no decision given before January 1, 2021 and PDCO has issued a negative opinion:** The MHRA will treat the application as refused; applicants can submit an updated PIP to the MHRA which addresses the reasons for refusal

- **Valid request for an EU-PIP or modification or waiver made to the EMA but no decision given before January 1, 2021 and PDCO has not yet given any opinion, or the UK disagreed with the PDCO opinion:** Submit the PIP to the MHRA, unless the applicant notifies the MHRA that they do not wish the application to proceed

    - EU-PIPs which become UK-PIPs under these transitional provisions will be referred to as adopted UK-PIPs in this guidance

    - New UK-PIP submissions after January 1, 2021 that have been assessed and agreed by the MHRA, will be referred to as agreed UK-PIPs

UK-PIP submissions after January 1, 2021:

- **Information should be provided on whether there is:**

    - an agreed EU-PIP and the opinion and supporting documentation is included;

    - an ongoing EU-PIP assessment, its timeline in the PDCO assessment cycle (i.e., day 30, 60, clock stop, day 90, or 120);

    - any scientific divergence between the submitted UK-PIP and the EU-PIP

- **Assessment pathways for UK-PIP submissions from January 1, 2021:** Annexes I and II

UK-PIP with agreed EMA opinion from January 1, 2021 or ongoing assessment at EMA from January 1, 2021:

- Positive PDCO opinion: The MHRA will aim to accept this

    - **The applicant may request a full assessment considering (but not restricted to) the following:**

- unmet UK paediatric needs;
- paediatric-only development particularly for an innovative product;
- the incidence of the disease in the UK population;
- the relevance of the scientific arguments by EMA/PDCO in the summary report (SR) to the UK paediatric population;
- any additional safety or efficacy concerns for the UK population;
- the nature and number of licensed products already available for the intended paediatric indication;
- the feasibility of performing the proposed paediatric studies in the UK only;
- PIP is to support a UK Paediatric Use Marketing Authorisation (PUMA)
    - **The applicant may request a full assessment**

- **PDCO opinion is negative:** Applicant has the option to withdraw the UK-PIP or continue with the MHRA assessment
    - **If the applicant chooses to continue with the MHRA assessment:** Consider incorporating changes to the UK-PIP during clock-stop, for the elements that received a negative PDCO assessment
        - **If the applicant chooses to withdraw the UK-PIP and a new UK-PIP is submitted:** The new PIP should be updated to address the reasons for refusal

UK-PIP with no EU-PIP from January 1, 2021: Full assessment of the UK-PIP is required

- **Additionally, the applicant should clarify if:**
    - there has been a previous negative EMA/PDCO PIP opinion;
    - there was a withdrawn EU-PIP prior to the adoption of an EMA/PDCO opinion;
    - the current UK submission has been updated since the previous negative or withdrawn EU-PIP;
    - the applicant has included the previously withdrawn or negative EMA/PDCO PIP SR as part of the supporting documents in the MHRA submission; or
    - during assessment, consideration will be given to the scientific discussions of the EMA/PDCO which led to the negative opinion or the withdrawal of the EU-PIP

PIP modifications

Modifications of an adopted or agreed UK-PIP:

- **When a PIP modification is submitted, it should confirm if there is:**

  - an agreed EU-PIP modification;
  - an EU-PIP modification assessment ongoing;
  - the modification submitted is for an adopted or agreed UK-PIP; or
  - a significant scientific divergence between the current agreed EU-PIP and the agreed UK-PIP

- **Modifications submitted for UK-PIPs where there is an EU-PIP:** Include the most recent PDCO opinion and PIP SR
- **Modifications submitted for agreed UK-PIPs:**
  - **Where the EU opinion for the initial UK-PIP was accepted by the MHRA:** Focused assessment
  - **Where the initial UK-PIP underwent full assessment:** Full assessment
    - **The applicant may request a full assessment**

UK-PIP modification of an agreed EMA opinion or ongoing assessment at EMA:

- **Positive PDCO opinion:** The MHRA will aim to accept this in cases where the initial UK-PIP was agreed on the basis of an agreed EU-PIP. However, divergence could occur as the MHRA will take decisions for PIPs based on national and NHS paediatric public health needs.
  - **A focused assessment may be needed considering (but not restricted to) the following:**
    - unmet UK paediatric needs;
    - paediatric-only development particularly for an innovative product;
    - the incidence of the disease in the UK population;
    - the relevance of the scientific arguments by EMA/PDCO in the SR to the UK paediatric population;
    - any additional safety or efficacy concerns for the UK population;
    - the nature and number of licensed products already available for the intended paediatric indication;
    - the feasibility of performing the proposed paediatric studies in the UK only; or
    - PIP is to support a PUMA
  - **Negative PDCO opinion whilst the UK assessment is ongoing:**
    - Applicant has the option to withdraw the UK-PIP modification request or continue with the MHRA assessment

- **If the applicant chooses to withdraw the UK-PIP modification request and a new UK-PIP modification is submitted:** The new UK-PIP modification request should be updated to address the reasons for refusal

- **If the applicant chooses to continue with the MHRA assessment:** The applicant can discuss amendments to the proposals before the final MHRA opinion on the proposed modification is agreed

UK-PIP modification with no agreed EU-PIP modification: A full assessment of modification will be required if there is no agreed EMA modification opinion

Submission of Paediatric Class Waivers

- **From January 1, 2021 the current EMA class waivers list will be adopted by the UK**
- **Positive EMA opinion on a class waiver request:** The MHRA will aim to accept this
- **No EMA opinion:** An MHRA assessment will be undertaken
- **Negative EMA opinion on whether a class waiver applies:**
    - applicant should submit a full product-specific waiver request for an MHRA assessment which should include an EMA opinion on the class waiver;
    - if there is an EMA opinion on the applicant's subsequent product-specific waiver request, then this should be made available to determine if a focused or full assessment is required

Compliance Check (CC)

Adopted UK-PIP CC:

- **Positive PDCO CC or interim CC:** Adopted as the UK CC outcome unless subsequent modifications have led to divergence between the UK-PIP and the EU-PIP
    - The applicant must pay particular attention to the agreed timelines of those measures which would need to be completed after the PDCO CC to ensure compliance on the date of the UK marketing authorisation (MA) submission
        - **PDCO compliance outcome documents:** Should be submitted ahead of, or at the time of, the MA application

Agreed UK-PIP CC:

- **No PDCO CC or any scientific divergence between the agreed UK-PIP and the EU-PIP:** UK assessment required for full or interim CC
- **Positive PDCO CC or the UK-PIP is equivalent to the EU-PIP:** The MHRA will adopt the PDCO CC outcome

- Applicants are encouraged to request a CC ahead of submission of an MA application where one is required for validation

- At completion of the CC procedure, the MHRA will issue compliance outcome documents

Noncompliance:

- **Due to (minor) administrative issues, or discrepancies that do not affect the scientific conduct of the study:** A streamlined assessment will be proposed at the time the applicant is informed of the noncompliance outcome

    - This will combine a shortened modification procedure with a rapid CC

- **If the above is not applicable:** The applicant will be required to submit a modification for a full assessment to align the noncompliant key elements of the opinion with those of the completed study report

    - A rapid CC will be offered at the end of a positive modification agreement

Statements of compliance:

- When all of the agreed PIP measures have been completed, will be issued, if appropriate, when an MA application (initial, extension, or variation) is granted

- The Summary of Product Characteristics and, where applicable, the package leaflet will include the results of the studies referred to in the UK-PIP

Paediatric Study Plans (PSP)

- **PSP agreed by the U.S. Food and Drug Administration:** Applicants should provide the agreed PSP as part of their UK-PIP submission

Unmet needs in the UK paediatric population

- Defined by:

    - therapeutic areas identified by UK health bodies as high-priority public health concerns;

    - product development in conditions identified after consultations with UK experts and patient groups, including those for rare diseases identified under the auspices of the Department of Health and Social Care (DHSC) policy paper — UK strategy for rare diseases;

    - product development in conditions (or paediatric groups) identified as critically important in the Paediatric Regulation 10-year report; and

    - products which are intended to be authorised as orphan medicines

    - products that fulfil the criteria of promising / innovative new products and are part of an accelerated MHRA submission or assessment pathway

- **Orphan Medicinal Products**

MHRA updates its guidance on orphan medicinal products in Great Britain

February 9, 2021

The MHRA has updated its guidance on how orphan medicinal products are regulated in Great Britain. The update adds a link to the Orphan Register, a list of authorised orphan medicinal products registered by the MHRA. See the updated guidance here.

Orphan medicinal products in Great Britain

December 31, 2021

The MHRA has published new guidance on how orphan medicinal products will be regulated in Great Britain after the end of the Brexit transition period. In contrast to the EU, the MHRA will review applications for orphan designation at the time of the marketing authorisation or variation application. See the guidance here.

How the MHRA Will Manage Orphan Medicinal Products From January 1, 2021

October 1, 2020

The MHRA has published new guidance on '**How the MHRA will manage orphan medicinal products from 1 January 2021 in Great Britain (GB)**' to help stakeholders prepare for the end of the transition period. The MHRA will offer incentives in the form of market exclusivity and full or partial refunds for marketing authorisation fees to encourage the development of medicines to treat rare diseases. This guidance was re-issued by the MHRA on December 31, 2020.

The new guidance covers the following matters:

- **Marketing authorisation application process for orphan designation:** The MHRA will be responsible for reviewing applications for orphan designation at the time of a marketing authorisation application. The following conditions must be satisfied: 1. Intended for the treatment, prevention, or diagnosis of a disease that is life-threatening or chronically debilitating; 2. Prevalence of the condition in Great Britain (GB) must not be more than 5 in 10,000; and 3. No satisfactory method of diagnosis, prevention, or treatment of the condition concerned exists in GB; satisfactory methods may include authorised medicinal products, medical devices, or other methods of diagnosis, prevention, or treatment which are used in GB
- **How to apply:** Applicants must send an **application form**, with their marketing authorisation application, specifically indicating in the cover letter their intention to seek an orphan designation
- **Decision on orphan status (as well as a decision of the marketing authorisation):** Made by the MHRA's advisory committee, the Commission on Human Medicines (CHM)); following the validation of the marketing authorisation application, a decision on orphan status will be made at the time of the decision on approval of the marketing authorisation
- **Appeal:** The applicant has the opportunity to appeal the decision to the CHM before the marketing authorisation is granted; the applicant should inform the MHRA of the intention to appeal as soon as possible
- **Market exclusivity from similar products in the approved orphan indication:** Up to 10 years from the date of first approval of the product in GB or EU/EEA; market exclusivity periods for

centrally authorised orphan medicine marketing authorisations that are converted to UK marketing authorisations will continue to apply'

- **Paediatric indications:** Orphan medicines authorised in GB with the results of studies from a paediatric investigation plan (PIP) included in the product information are eligible for **an additional two years of market exclusivity**
- **Variation applications (section 4.1 of the Summary of Products Characteristics):** The orphan criteria will be assessed in parallel to the approval of the new indication; a new period of market exclusivity is only given if the applied for therapeutic indication falls within a new orphan condition
- **Fees:** No additional fees for orphan designation application
- **SME status:** Waiver from scientific advice fees will also be available for UK based SMEs; companies who have, or intend to seek, SME status should ensure that they have the relevant documentation in place if an SME fee refund is to be applied for
- **Orphan register:** All medicines that gain a GB orphan marketing authorisation will be listed on the GB Orphan Register (active and then withdrawn, suspended or expired)

- **Generic Medicines**

Reference Medicinal Products and Comparator Products in Bioequivalence/Therapeutic Equivalence Studies from January 1, 2021

September 1, 2020

The Medicines and Healthcare products Regulatory Agency (**MHRA**) has updated its **guidance** on 'Reference Medicinal Products' (**RMPs**) to inform of changes to the legislation of RMPs used to support abridged marketing authorisation applications from January 1, 2021. This guidance will apply from January 1, 2021 in line with the latest **Human Medicines Regulations** (Amendment etc.) (EU Exit) Regulations 2019 (the **Regulations**) and makes reference to the MHRA **guidance** on Comparator Products in Bioequivalence/Therapeutic Equivalence studies (**CPs**) from January 1, 2021 (of which applications relating to biosimilars are out of the scope). On December 31, 2020 the MHRA re-issued guidance on Reference Medicinal Products, as well as guidance on comparator products in Bioequivalence/Therapeutic Equivalence studies.

The updates to the guidance cover the following matters:

- **Regulatory Data Protection and Market Exclusivity Periods:** Regulatory Data Protection and market exclusivity period entitlements for RMPs approved before January 1, 2021 will continue to apply in the UK

- **Great Britain:** Any applications of RMPs for new generic medicines or other abridged marketing authorisation submitted after January 1, 2021 will need to fall within the definition in **regulation 48** of the Regulations; the Regulations, which will be updated to reflect the change of implementation dates following the transition period, will include: (i) products that are, or have been, authorised for at least eight years in the UK (including those authorised by conversion from EU marketing authorisations); and (ii) products that had an EU marketing authorisation on January 1, 2021 but which did not convert into Great Britain marketing authorisations as the holder opted out of that process

- **Northern Ireland:** As the **EU medicines legislation** will remain applicable in Northern Ireland, RMPs included in marketing authorisation applications submitted into Northern Ireland should comply with relevant EU legislation; for Northern Ireland, the definition of a RMP in **regulation 48** of the Regulations includes UK-authorised products and products in relation

to which: (i) there is an EU-marketing authorisation; or (ii) in relation to which a Competent Authority of an EEA State has granted a marketing authorisation; applicants seeking UK-wide marketing authorisations (Great Britain and Northern Ireland) will be required to comply with requirements applicable in Northern Ireland (namely EU law)

- **Authorisation Validity Based on 'European Reference Medicinal Product':** Authorisations based on a 'European Reference Medicinal Product', as described in Article **10.1** of Directive 2001/83 (as amended), that have been granted, and applications that have been submitted to MHRA prior to January 1, 2021, will continue to be valid; however, for applications submitted to MHRA from January 1, 2021, the RMP will need to fall within the definition in **regulation 48** as mentioned above

- **Non-Great Britain Comparator Products:** Where a **CP** used in bioequivalence and therapeutic equivalence studies is not sourced from Great Britain, the applicant should provide evidence that it is representative of the RMP. The CP should be authorised in and sourced from a country with similar scientific and regulatory standards as the UK (such as the EU/EEA, Switzerland, USA, Canada, Australia, and Japan) and would normally be expected to be:

    - part of the same global marketing authorisation (GMA) as the RMP; or

    - marketed in the country of origin through a licensing arrangement with the innovator company or corporate entity that currently markets the medicine in Great Britain.

- **Identical Applicability of the GMA Concept in Great Britain and the EU:** The GMA contains the initial authorisation and all variations and extensions; it includes any additional strengths, pharmaceutical form, administration routes or presentations authorised through separate procedures and under a different name, granted to the Marketing Authorisation Holder (MAH) of the initial authorisation

- **Identicality vs. Representativeness:** The non-Great Britain CP used is required to be representative of the RMP, but it is not required to be identical to it. Certain minor differences between both products may be accepted, if justified and provided this is supported by bridging data, which could include but are not limited to:

    - Colour of tablet coatings (assuming no difference in functionality of coat) or capsule shells;

    - Scorelines, embossings, and imprintings on solid dosage forms;

    - Flavours in liquid dosage forms; and

    - Container closures.

- **Demonstration of Identicality of the Non-Great Britain CP to the RMP:** In cases where the applicant provides written confirmation from the MAH of the non-Great Britain CP that the CP is identical to the RMP, no further analytical data are required, and the use of this identical non-Great Britain CP is also acceptable for more complex formulations; for the drug substance and finished products specifications, non-significant differences in specifications may be acceptable if fully justified. The written confirmation should confirm the following are identical in both products:

    - the route of synthesis of the drug substance(s);

- the drug substance specifications;
- the finished product quantitative composition;
- the manufacturing process including in-process controls;
- the finished product specifications; and
- the stability data.

- **Demonstration of Representativeness of the Non-Great Britain CP to the UK RMP:** If a CP authorised and sourced from outside Great Britain is used, the applicant should provide adequate data or information to scientifically justify the relevance of these comparative data and establish an acceptable bridge to the RMP. As a scientific matter, the type of bridging data needed should always include data from analytical studies that compare all three products between:
  - the RMP and the non-Great Britain CP to establish suitability of the latter as CP in BE/TE studies;
  - the proposed medicinal product and the RMP to demonstrate similarity to allow bridging of the RMP data; and
  - the proposed medicinal product and the non-Great Britain CP to support the BE/TE studies.

Any observed differences in the data have to be duly justified with regard to their potential impact on safety and efficacy.

- **Required Information for the RMP and Non-Great Britain CP:** The required Information in Module 1.5.2 of the Common Technical Dossier structure for both the RMP and non-Great Britain CP includes:
  - Name and address of the authorisation holder of the non-Great Britain CP used, the product name, the country of authorisation, country of origin, and authorisation number;
  - Proof of purchase (batch number, date and place of purchase, and expiry date);
  - Samples in their original container closure systems should be available upon request;
  - Product information (summary of product caracteristics or equivalent);
  - Certificates of analysis (tested according to the proposed specification for the proposed medicinal product);
  - The excipients in the formulation of the RMP, when compared to the non-Great Britain CP, should be qualitatively the same. Any differences in excipients would need to be shown to have no effect on safety or efficacy; and
  - If quantitative formulation information is available for these two products it should also show the non-Great Britain CP to be representative of the RMP.

The experimental comparison should include the physico-chemical properties and all critical product attributes of the medicinal product; these should include device attributes where appropriate. Where provided, dissolution data should cover the physiological pH range.

- **Number of Batches to Be Tested:** For the comparison between the RMP and the non-Great Britain CP, data on at least three batches of each product would usually be expected; in cases of products that exhibit a higher inherent batch-to-batch variability or that are complex, a larger number of batches might be required to establish representativeness

- **Analytical Methods:** The precision and accuracy of the analytical methods and the inter-batch variability are critical to deciding if the formulations of the RMP and non-Great Britain CP are representative of each other; the analytical methods and analytical method validation reports used to generate the physicochemical data should be provided to satisfy this requirement

- **Acceptability of Approach:** The overall acceptability of such an approach and the type of bridging data needed will be a case-by-case/product-type decision and is recommended to be discussed upfront with MHRA if one or more of the following applies to the product:

    - does not exhibit immediate release of the drug substance;
    - is not for oral administration;
    - is made by complex methods of manufacture;
    - exhibits a narrow therapeutic range or safety margin (for example, careful dosage titration or patient monitoring);
    - has a steep dose-response relationship;
    - a risk of serious undesired effects;
    - complicated or variable pharmacokinetics (such as nonlinear pharmacokinetics, variable or incomplete absorption);
    - an absorption window (i.e., site-specific absorption); or
    - substantial (e.g., greater than 40%) first-pass metabolism.

- **Biosimilar medicinal products**

MHRA Draft Guidance on the Licensing of Biosimilar Products From January 2021

October 7, 2020

The MHRA has drafted new **guidance** on "The licensing of biosimilar products" to provide developers of similar biological medicinal products (biosimilars) with a clear outline of the requirements for biosimilar products in the UK following the end of the transition period.

The new guidance is mainly based on the current CHMP (Committee for Medicinal Products for Human Use) **guidelines**. Some distinct key features are:

- **UK reference products:** The Reference Product (RP) should comply with **Regulation 48** of the Human Medicines (Amendment, etc.) (EU Exit) Regulations 2019; the UK RP (or an RP representative of the UK product) must be used for the required comparability studies which could include an EU RP with evidence that the RP is licensed in the EU via the centralised procedure; in order to use a non-UK RP in clinical studies, evidence should be provided that the non-UK RP is representative of the UK RP; data and market exclusivity period entitlements for RPs approved before the date of EU exit will continue to apply in the UK. It is interesting to note that all non-UK RPs must be authorised in and sourced from a country with similar scientific and regulatory standards as the UK (examples would be EU/EEA countries, Switzerland, United States, Canada, Australia, and Japan).
  RPs include:

    - products that are, or have been, authorised for at least eight years in the UK (including those authorised by conversion from EU marketing authorisations);

    - products that had an EU marketing authorisation at the end of the transition period, but which did not convert into a UK product licence, as the marketing authorisation holder opted out of the process; and

    - products for which an EU marketing authorisation had ceased to be in force before the end of the transition period, for reasons not relating to quality, safety, or efficacy.

- **Biosimilarity principles:** A biosimilar should be highly similar to the RP in physicochemical properties, biological activity/potency, and clinical profiles; biosimilar development requires that the impurity profile and the nature of excipients of the biosimilar itself do not give rise to concerns; any observed differences must be duly justified with regard to their potential impact on safety and efficacy; the biosimilar must have the same molecular and biological structure and the same posology and route of administration.

  Importantly, there is no regulatory requirement to repeat the demonstration of biosimilarity against the RP (for example, in the context of a change in the manufacturing process) once a UK product licence for the biosimilar has been granted.

- **No requirement for in vivo studies in animals:** No in vivo studies in animals are requested to be submitted to the MHRA for consideration of a UK licence for a biosimilar product as these are not relevant for showing comparability between a biosimilar candidate and its RP; conduct of in vivo studies in animals does not contribute to resolving the possibility that a biosimilar candidate may not be highly similar to the RP and in vivo studies should not be done with this intent.

- **Changes in the requirement for a comparative efficacy trial in most cases:** A comparative efficacy trial is not considered necessary in most cases; a well-argued justification for the absence of an efficacy trial, supported by sufficient comparative analytical and functional data, should be included in the submitted application; there may still be cases requiring a comparative efficacy/safety trial, for example, where it is difficult to predict the impact of analytical differences which have not been resolved by adaptations to the manufacturing process; exceptionally, additional clinical safety data may be required where safety uncertainties cannot be resolved without patient exposure pre-licensing.

- **No requirement for repeat demonstration of biosimilarity:** There is no regulatory requirement to repeat the demonstration of biosimilarity against the RP once a UK product

licence for the biosimilar has been granted (for example, in the context of a change in the manufacturing process).

- **Relation to other guidelines:** The MHRA offers some flexibility in relation to guidelines applicable in other jurisdictions in relation to in vivo studies: the content of Module 4 for the UK can be limited to those studies that are GLP compliant, requirements of other regulators notwithstanding; Module 4 in the UK may not be part of the CTD supporting the product in other regions and the MHRA will accept this deviation.

- **Risk management plan (RMP):** Where ongoing additional pharmacovigilance activities are required for the RP (for example, participation in ongoing disease registries), these should also apply to the biosimilar candidate, preferably through collaboration or participation in those studies or registries already in place for the RP to enable collection of real-world information to support signal detection of potential safety signals related to the RP and its biosimilars; any additional risk minimisation measures that continue to be required for the RP should also be implemented for the biosimilar candidate, for example educational materials for healthcare professionals and patients or patient alert cards.

- **Interchangeability:** Once a biosimilar is authorised, it is considered interchangeable with the RP, which means that a prescriber can choose the biosimilar over the RP (or vice versa) and expect to achieve the same therapeutic effect (however, like all biologicals, biosimilars must be prescribed by brand name); substitution at the pharmacy level without consulting the prescriber is not permitted for biological medicines, including biosimilars.

- Clarification about this guidance can be sought by sending an email to MHRA in the first instance: **biosimilars@mhra.gov.uk** or by seeking MHRA scientific advice.

- **Traditional Herbal and Homeopathic Medicines**

Guidance on How Traditional Herbal Medicines and Homeopathic Medicines Will Be Treated by the Medicines and Healthcare Products Regulatory Agency (MHRA) from January 1, 2021

November 4, 2020

The MHRA has published new **guidance** titled "Guidance on new provisions for traditional herbal medicinal products and homoeopathic medicinal products from January 1, 2021." This guidance will apply from January 1, 2021 in line with the Human Medicines Regulations (Amendment etc.) (EU Exit) Regulations 2019. This guidance was re-issued by the MHRA on December 31, 2020.

The guidance covers the following matters:

- **Traditional herbal medicines:** Prior to January 1, 2021, the MHRA may expand the list of countries from which it will accept evidence for traditional herbal medicines

    - **Currently:** For traditional herbal registration, evidence has to be provided that the product or a corresponding product has been used for a period of 15 years within the EU/European Economic Area (EEA)

    - **From January 1, 2021:** The MHRA may be able to accept the 15 years of traditional evidence from a wider range of countries in addition to EEA countries

        - **Suitable countries:** Level of pharmacovigilance equivalent to that of the UK; the MHRA will publish a list of suitable countries which will be updated as new entries arise

- **Traditional herbal medicines intended to be marketed in Northern Ireland:** Traditional use evidence will need to be provided that the product or a corresponding product has been used for a period of 15 years within the EU/EEA

- The MHRA may publish its own list of herbal substances, preparations, and combinations for use in traditional herbal medicines; this will include the entries in the existing EU list and the MHRA list will be updated as new entries arise

    - Only the EU list will be relevant for applicants wanting to apply to market a traditional herbal medicine in Northern Ireland

- **Homeopathic medicines:** From January 1, 2021, the definition of a homeopathic medicinal product will be expanded

    - The definition will cover products prepared from homoeopathic stocks made in accordance with a homoeopathic manufacturing procedure described in the European Pharmacopoeia or, in the absence of a description there, in accordance with a procedure described in the British pharmacopoeia or in a pharmacopoeia used officially in a country that is included in a list published by the MHRA

    - The list will include the:

        - British Pharmacopoeia

        - European Pharmacopoeia

        - Pharmacopoeia used officially in an EEA country

            - This list will be updated as new entries arise

- **Homeopathic medicines to be marketed in Northern Ireland:** The current EU definition of a homeopathic medicinal product will remain

- **Issues relating to place of establishment, variations, and other regulatory issues which would previously have been regulated at the EU-level:** Refer to the **guidance on marketing authorisations (MAs)**

- **Human Organs, Tissues and Cells**

December 31, 2020

MHRA publishes guidance on quality and safety of human organs, tissues and cells

The MHRA has published guidance for hospitals, tissue establishments and fertility clinics for ensuring the quality and safety of human organs, tissues and cells (including reproductive cells). See the guidance here.

- **Quality and Safety of Blood and Blood Components**

Guidance for Blood Establishments, Blood Banks, and Manufacturers of Blood Products on Ensuring the Quality and Safety of Blood and Blood Components from January 1, 2021

November 6, 2020

The DHSC has published new **guidance** titled "Quality and safety of human blood and blood components from January 1, 2021." The MHRA re-issued this guidance on December 31, 2020.

- **Supply of Medicines**

December 31, 2020

MHRA updates guidance on reporting requirements for medicine shortages and discontinuations

The MHRA has updated its guidance on reporting requirements for medicine shortages and discontinuations to add a list of contacts for questions about ensuring the flow of medical supplies into the UK. See the guidance here.

Department of Health and Social Care Sends Letter to Suppliers of Medicines and Medical Products to Urge Supply Continuity Planning

November 17, 2020

The Chief Commercial Officer of the Department of Health and Social Care (DHSC), Steve Oldfield, has written a letter to medicines and medical product suppliers urging them to 'act now' to prepare for the new customs and border controls that will be imposed on January 1, 2021. To help address the new border challenges, the DHSC has asked suppliers to respond to questionnaires and data requests it has sent out 'as quickly as you are able' otherwise 'we cannot effectively work together to mitigate the risk of delay and disruption at the short straits'. As a way of reducing the potential for disruption, the UK is planning to phase in the border controls on this side of the Channel. However, the government does not have control over the checks that EU member states impose at the EU border, and the biggest potential cause of disruption is 'traders not being ready for controls implemented by EU member states on January 1, 2021'. See the letter **here**.

UK Government Secures Critical Freight Flow for Medicines as United Kingdom Nears End of Transition Period

October 13, 2020

The Department for Transport has published a **press release** titled "Government secures critical freight flows as UK nears end of transition period."

The UK government has signed four contracts with ferry operators that will help to ensure that vital medical supplies and other critical goods will continue to be delivered into the United Kingdom, regardless of the outcome of the negotiations with the European Union.

The press release covers the following details:

- The four contracts with ferry operators will provide capacity equivalent to over 3,000 HGVs per week, mitigating the risk of disruption as the United Kingdom and European Union adjust to new border processes at the end of the transition period
- The contracts have been signed with: Brittany Ferries, DFDS, P&O, and Stena Line

- Collectively, the contracts are worth £77.6 million
- Contract length: Up to six months after the end of the transition period
- The contracts have been awarded through the government's Freight Capacity Framework

- **Supply of medicinal products to and from Northern Ireland**

January 8, 2021

Unilateral Declarations of the EU and the UK on the application of Union law related to medicinal products in respect of Northern Ireland after the end of the transition period

The UK and the EU have made unilateral declarations on the application of Union law related to medicinal products in respect of Northern Ireland after the end of the transition period. See the declarations here.

January 5, 2021

MHRA publishes guidance on supplying over-the-counter medicines to Northern Ireland

The MHRA has published guidance explaining how the supply of medicines into Northern Ireland works. See the guidance here.

December 23, 2020

Commission issues notice on the application of the Union's pharmaceutical acquis in markets historically dependent on medicines supply from or through Great Britain after the end of the transition period

The European Commission has issued a helpful notice which provides for transitory measures allowing Cyprus, Malta, Ireland and Northern Ireland (i.e.. EU territories that have historically dependent on medicines supply from or through Great Britain) to depart from the EU pharmaceutical legal framework in some specific areas. The derogation is effective from January 1, 2021 until December 31, 2021.

MHRA Issues Guidance on What You Need to do to Supply Investigational Medicinal Products from Great Britain to Northern Ireland from January 1, 2021

December 11, 2020

The MHRA has published guidance explaining the requirements that need to be satisfied in order to supply investigational medicinal products from Great Britain to Northern Ireland. See the guidance **here.** The MHRA re-issued this guidance on December 31, 202.

MHRA Issues Guidance on What You Need to do to Supply Authorised Medicines from Great Britain to Northern Ireland from January 1, 2021

December 11, 2020

The MHRA has published guidance explaining the requirements that need to be satisfied in order to supply authorised medicines from Great Britain to Northern Ireland. See the guidance **here.**

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Supplying Authorised Medicines from Great Britain to Northern Ireland from January 1, 2021

October 27, 2020

The MHRA has published new **guidance** on "Supplying medicines to Northern Ireland from 1 January 2021" to help wholesale dealers or manufacturers in Great Britain sell or supply authorised medicines to authorised persons in Northern Ireland following the end of the transition period. This guidance was re-issued by the MHRA on December 31, 2020.

The new guidance covers the following matters:

- **Supply of authorised medicines from Great Britain to Northern Ireland until December 31, 2021:**
    - **EU rules on importation and unique identifier requirements:** Pragmatic approach until December 31, 2021
        - **Batch testing and QP certification:** Continue to be required to place a product on the UK market
            - Done in Great Britain: Will enable supply to Northern Ireland until December 31, 2021
            - Done in the EU/EEA: Will enable supply to Northern Ireland via Great Britain (including packs not moved under transit procedures using the Common Transit Convention) until December 31, 2021
            - Until December 31, 2021 medicines can be supplied from the Great Britain market to Northern Ireland without requiring regulatory importation controls (manufacture and import authorisation, batch testing and QP certification done in Northern Ireland or an EEA state); wholesale dealers can continue to supply medicines from Great Britain to Northern Ireland for an additional 12 months beyond the end of the transition period
        - **Serialisation requirements of EU Delegated Regulation 2016/161:** Continue in Northern Ireland from January 1, 2021; medicines with a marketing authorisation valid in Northern Ireland will require a unique identifier and a tamper evident device on each pack
            - Until December 31, 2021 the unique identifiers on packs with a marketing authorisation valid in NI (including UK-wide MAs) supplied by a manufacturer or wholesaler in the EEA will not require decommissioning when exported to the UK; unique identifiers on these packs should be decommissioned in Northern Ireland as required by EU Delegated Regulation 2016/161
            - Medicines with a marketing authorisation valid only in Great Britain: Will not require a unique identifier; may be voluntarily placed on GB packs, however, these do not require upload as there is no obligation and will be no capability to decommission in GB
                - Companies encouraged to retain the tamper evidence device
    - **Apart from these 2 areas**: Medicines for Northern Ireland must follow the EU acquis as per the Northern Ireland Protocol
- **The following importation controls done in Northern Ireland or an EEA state will be required for the supply of authorised medicines from Great Britain to Northern Ireland from January 1, 2022:**
    - Importation via a Manufacture and Importation Authorisation (MIA) holder
    - Batch testing

    - Certification by a Qualified Person
- From January 1, 2022 the unique identifiers on UK packs exported to Great Britain by a manufacturer or wholesaler in the EEA will require decommissioning
    - If these packs are later supplied to Northern Ireland: New unique identifiers should be applied to packs and uploaded to the EU medicines verification hub, unless they were placed on the market before 11pm on December 31, 2020
- The additional flexibilities for importation and serialisation requirements until December 31, 2021 do not impact on the timing of Article 41 which will only apply for medicines placed on the market before 11pm on December 31, 2020
    - It is important to note that the additional flexibilities for importation and serialisation requirements until 31 December 2021 do not impact on the timing of Article 41 which will only apply for medicines placed on the market before 11pm on 31 December 2020.
- Supply chains should prepare for changes to Northern Ireland supply routes before January 1, 2022; there are other supply chain options that will not require importation controls to be performed in Northern Ireland or an EEA state, including:
    - use of the Common Transit Convention when transporting goods via Great Britain
    - routing Northern Ireland logistics directly from the EEA
    - changing the location of batch testing and QP certification activities
- **Supply of medicines that are on the market before 11pm on December 31, 2020:** Article 41 of the EU Withdrawal Agreement states that goods placed on the market in the European Union or the United Kingdom before the end of the transition period may continue to circulate between these two markets from January 1, 2021; this includes medicines moving from Great Britain to Northern Ireland. A medicine is "placed on the market" if it is available for sale or supply and there has been a written or verbal agreement (or offer of an agreement) to transfer ownership of the medicine to another legal entity; placing a manufacturing order for completion after 11pm on December 31, 2020 is insufficient to qualify for continued circulation, the medicine must have been manufactured and QP certified.
- **Medicines placed on the market in the European Union or United Kingdom before 11 p.m. on December 31, 2020:**
    - **Article 41 of the EU Withdrawal Agreement enables these batches to remain available for sale or supply between Great Britain, Northern Ireland, and the European Union after January 1, 2021, without additional regulatory checks if they meet the following requirements:**
        - 1. Manufactured;
        - 2. Certified by a Qualified Person (QP);
        - 3. Made available for sale or supply in the manufacturer's or wholesaler's stock management system
    - **Additionally, before 11 p.m. on December 31, 2020, one of the following requirements must be met:**
        - The medicine must have transferred ownership by sale or supply to another legal entity
        - An offer to either purchase or take ownership of the medicine must have been made to the manufacturer or wholesaler by another legal entity (in this case the actual transfer of ownership may take place after 11 p.m. on December 31, 2020)
            - This may include transfer of stock for sale or supply to different legal entities in the same company group
    - **A medicine already in the supply chain before 11 p.m. on December 31, 2020:** Can continue to be sold under Article 41 without further regulatory checks

        - Such as one stored by a wholesaler in the United Kingdom or the European Union who has been sold or supplied the medicine (thus transferring ownership)
- **Placing a manufacturing order for completion after 11 p.m. on December 31, 2020:** Insufficient to qualify for continued circulation; the medicine must have been manufactured and QP certified
- **Checks required prior to sale or supply to confirm medicines were placed on the market before 11 p.m. on December 31, 2020:** Prior to agreeing to supply the products, the wholesale dealer or manufacturer in Great Britain will be responsible for confirming that the person to be supplied in Northern Ireland is authorised to receive the product; medicines placed on the market before 11 p.m. on December 31, 2020, may be supplied to a wholesaler or other authorised person in Northern Ireland; manufacturers are encouraged to ensure that the date of placing on the market is visible to the supply chain
    - **Checks should be performed to confirm that a medicine has met the "placed on the market" criteria:** Manufacturer or wholesaler in Great Britain may either:
        - Confirm that each batch of medicine has met all of the relevant criteria for being placed on market as listed above; or
        - Confirm that ownership of the medicine has transferred between two UK or EU legal entities before 11 p.m. on December 31, 2020; this alone would suffice, as a medicine cannot legally be sold or supplied unless all the steps above have been met
    - **Examples of evidence to confirm that a batch has been placed on the market before 11 p.m. on December 31, 2020:** A written statement from the manufacturer or a wholesaler who has sold or supplied the batch or a reference to company internal systems that shows batch certification (e.g., global enterprise resource planning system); other forms of evidence are acceptable
- **Case studies to help clarify when a medicine has been "placed on the market":**
    - **Case Study 1:**
        - Before the end of the transition period: Medicine has been QP certified and is in manufacturer's or wholesaler's warehouse; for stock management reasons, the batch is "on hold" in the warehouse inventory system
            - CONCLUSION: Not been placed on the market
                - Not available for sale or supply
                - If the batch were marked in the warehouse system as available to supply customers when orders are received, this would qualify for the purposes of provisions under Article 41, only once an agreement (or offer of such an agreement) to transfer ownership for sale or supply of the medicine from the manufacturer or wholesaler to another legal entity has taken place
    - **Case Study 2:**
        - Before the end of the transition period: Medicine has been QP certified and is physically located in manufacturer's or wholesaler's warehouse in an EU state; it is marked as available for sale or supply in the warehouse system; the ownership of that medicine then is transferred over to the UK affiliate, which is a separate legal entity from the original owner
            - CONCLUSION: Placed on the market and would qualify for provisions under Article 41; it could be supplied to Northern Ireland after the end of the transition period
    - **Case Study 3:**

        - Before the end of the transition period: Medicine has been QP certified and is physically located in manufacturer's or wholesaler's warehouse in an EU state; it is marked as available for sale or supply in the warehouse system; a separate legal entity to the manufacturer or wholesaler offers to either purchase or take ownership of the medicine before 11 p.m. on December 31, 2020; the sale or transfer of ownership is not complete before 11 p.m. on December 31, 2020
            - CONCLUSION: Placed on the market and would qualify for provisions under Article 41; it could be supplied to Northern Ireland after the end of the transition period
    - **Case Study 4:**
        - Before the end of the transition period: Medicine has been QP certified and is physically located in manufacturer's or wholesaler's warehouse in an EU state; it is marked as available for sale or supply in the warehouse system; ownership of the medicine has not transferred to another legal entity before the end of the transition period; no offer has been made by another legal entity to the manufacturer or wholesaler to take ownership of the medicine before the end of the transition period
            - CONCLUSION: Not been placed on the market
                - Ownership has not transferred to another legal entity or an offer has not been made to the manufacturer or wholesaler by another legal entity
    - **Case Study 5:**
        - Before the end of the transition period: Medicine has been QP certified and is physically located in manufacturer or wholesaler's warehouse in the United Kingdom; it is marked as available for sale or supply in the warehouse system; ownership of the medicine is transferred to a different legal entity, e.g., a company affiliate in the European Union; ownership is then transferred back to the wholesale or manufacturer (the second transfer of ownership could either take place before or after the end of the transition period)
            - CONCLUSION: Placed on the market and would qualify for provisions under Article 41; ownership has transferred to another legal entity before the end of the transition period, and it is available for sale or supply
    - **Case Study 6:**
        - Before the end of the transition period: Medicine has been QP certified and is physically located in manufacturer or wholesaler's warehouse in the United Kingdom; ownership of the medicine is transferred to a different legal entity, e.g., a company affiliate in the European Union; the batch is pre-allocated to supply a specific market (e.g., Northern Ireland)
            - CONCLUSION: Placed on the market and would qualify for provisions under Article 41; ownership has transferred to another legal entity, and it is available for sale or supply
- **Licensing requirements for medicines containing controlled drugs from January 1, 2021:** There will be no changes; this is covered by UK legislation
    - Controlled drugs are controlled in the UK under the Misuse of Drugs Act 1971 ('the 1971 Act') and the Misuse of Drugs Regulations 2001 ('the 2001 Regulations')
    - From January 1, 2021 Home Office controlled drug import-export licensing requirements for trade in controlled drugs within the UK will not change

  - Home Office controlled drug import-export licensing requirements for trade in controlled drugs from the UK, including from Northern Ireland, to the EU, and vice versa, will not change
  - There will be no new licensing requirements under the 1971 Act for companies moving medicines containing controlled drugs from Great Britain to Northern Ireland as a result of the Protocol
    - See guidance on how to apply for a Home Office controlled drug import-export licence for trade in controlled drugs from the UK.

- **Collaboration with other Regulators of Medicinal Products**

July 12, 2021

There has been an update to GOV.UK guidance on "***Medicines: get scientific advice from MHRA***", which sets out the following:

Summary

- Scientific advice can be requested from the MHRA at **any stage of the initial development** of the medicine, including:
  - before submission of the application for an MA
  - during the pre-submission period for a variation to an existing MA
- Meetings can also be held with the MHRA to discuss:
  - pharmacovigilance
  - advertising
  - proposals to change labelling or package leaflets
  - post-authorisation regulatory advice relating to a product range
- A **broader scope** of scientific advice can also be requested, which would cover broader issues and not relate to only 1 development programme or product.
- A **joint meeting** with MHRA and NICE can be requested.
- Scientific advice given by MHRA is **not legally binding** for any future application of the product discussed, either on the part of MHRA or the company.
- MHRA scientific advice cannot be taken as indicative of any future agreed position.
- MHRA's answers are **based on the submitted questions and documentation** and does not account for future changes and developments in scientific knowledge or regulatory requirements.

Types of advice

- The questions asked by the sponsor to the MHRA must be as **precise and clear** as possible.
- The questions should **address specific scientific issues** on:
  - quality aspects (for example, the chemical, pharmaceutical and biological testing necessary to demonstrate the quality of a medicinal product)
  - non-clinical aspects (for example, the toxicological and pharmacological testing necessary to demonstrate the safety of a medicinal product)
  - clinical aspects (for example, endpoints, trial duration, target population, choice of comparator etc.)
  - pharmacovigilance plans and post-authorisation safety study protocols
  - an application for a variation or renewal
  - advice before publishing advertising for a medicinal product
  - changes to labelling of packaging leaflets for medicinal products or a product range

- The questions should be **prospective** and **concern the future development** of a medicinal product.

Broader scope meetings

- A broader scope meeting is not a **product-specific request**. Examples of this include:
  - general approaches to product development
  - overall product development plans where there are very broad issues that may go beyond what can be discussed at a routine scientific advice meeting
  - complex issues of drug/device combination products
  - choice (including relative pros and cons) of study endpoints in particular indications
  - practical issues of study design, management and analysis
  - risk management plans and other post-licensing aspects
  - legal reclassification of products from prescription-only medicine to pharmacy medicine or from pharmacy medicine to general sales list.
- The MHRA require **briefing material** for broader scope meetings before the meeting and a general idea of the sorts of issues / questions the sponsor wishes to discuss.
- A broader scope meeting is less structured than typical scientific advice or pharmacovigilance advice meetings.
- It may be appropriate for the sponsor to give an extended presentation to allow for discussion around the issues raised.
- Meetings are planned for up to **90 minutes**.
- These meetings may include a variety of contributors including external experts and lay or patient representatives.
- Either or both parties can invite participants.
- The overall composition of the meeting is by mutual agreement.
- The MHRA charges a fee for broader scope meetings.
- As these meetings are more wide-ranging and more speculative, the MHRA does not give written advice after the meeting.
- These meetings are **requested in the same way** as standard scientific advice meetings.

Meetings with MHRA and NICE

- A **joint scientific advice meeting** with the MHRA and NICE can be requested.
- At these meetings a sponsor can discuss a clinical study design that can **satisfy regulatory and NICE requirements**.
- Optional input from can also be requested from the Clinical Practice Research Datalink.
- Following the meeting, the MHRA and NICE produce **separate advice documents** to answer the respective questions raised.

See here an example case study detailing a successful joint scientific advice meeting that the MHRA and NICE had with the University of Birmingham.

Requesting scientific advice

- An MHRA - Request for scientific advice form must be submitted to scientific_advice@mhra.gov.uk.
- On the form the following should be included:
  - therapeutic area
  - scope of advice being sought

  - number of company staff expected to attend (limited to 4 for a meeting with the MHRA Division of Vigilance and Risk Management of Medicines)
  - preferred meeting dates and dates to avoid
  - a draft list of the proposed questions
- A mutually-agreed date is then set.

Documents

- The final briefing document including the documents listed below should be delivered to MHRA **no less than 10 working days** before the date of the meeting:
  - the final proposed questions together with the position on each question in Word format
  - an electronic copy of any presentation to be given at the meeting
  - any appendices
  - labelling and leaflet artwork examples if the meeting is about changes to labelling and leaflets for a product or range of products
- Any appendices, if relevant, should be limited to essential information and can include:
  - background information
  - information relating to the questions (for example, relevant study protocols)
  - content of previous scientific advice received (MHRA relevant international authorities)
  - relevant guidelines

The meeting

- The MHRA prefer to have **face-to-face meetings** but video conferencing may be arranged in exceptional circumstances.
- Telephone and teleconference meetings are generally not considered satisfactory to discuss complex scientific and regulatory issues.
- MHRA staff review the documentation before the meeting and either have **provisional advice** or **further questions** and clarification for the meeting.
- A sponsor can give a brief presentation but this should be kept as short as possible (usually only 10 to 15 minutes) to allow maximum time for discussion.
- Only in exceptional circumstances should any information not in the briefing document be presented.
- The meeting will normally **last no more than 90 minutes**.
- The sponsor should take **notes of the meeting**.

After the meeting

- The MHRA sends its answers to the questions **within 30 working days** of the meeting.
- A sponsor should send the notes of the meeting **within 15 working** days of the meeting (for information only and not to be commented on).
- The **final advice** will be provided in the MHRA advice letter.
- A sponsor can ask the MHRA to **clarify the advice given**, which will be done by email or teleconference.
- The clarification does not cover the impact of the advice on other aspects of the development plan or on other development strategies considered in the light of the advice received.
- Subsequent meetings and follow-up meetings will be charged at the same rate as the initial meeting (subject to the scope of the advice requested).

- The advice provided is without prejudice to applicable legislation relating to particulars and documents which should be submitted in support of any marketing authorisation (or other) application.
- The advice provided is also without prejudice to any intellectual property rights to third parties.

Fees

- Fees are charged for scientific advice.
- Meetings requested by MHRA or covered by agreed waivers are not charged.
- The sponsor is invoiced for the scientific advice after the meeting.
- A waiver from scientific advice fees is available to UK based Small and Medium-Sized Enterprises as set out in the Human Medicines (Amendment etc.) (EU Exit) Regulations 2020.
- The MHRA Fees Regulations provides option for 'small companies' to apply for payment easement. Applications for SME status must be made prior to submitting an application for a scientific advice meeting.
- Once the SME status is approved, the company must then submit the approval letter from the MHRA Finance department with their scientific advice meeting application.

February 9, 2021

MHRA Updates its Guidance on the Access Consortium's New Active Substance (NAS) Work Sharing initiative

The MHRA has updated its guidance on the Access Consortium's New Active Substance (NAS) Work Sharing Initiative to add the Expression of Interest form. See the updated guidance here.

January 5, 2021

UK MHRA and VMD enters into interim Canada-United Kingdom Trade Continuity Agreement with the Regulatory Operations and Enforcement Branch of Health Canada

The UK MHRA and Veterinary Medicines Directorate has announced that they have entered into an interim Canada-United Kingdom Trade Continuity Agreement with the Regulatory Operations and Enforcement Branch of Health Canada. Under this interim agreement, Canada and the UK will continue to recognise Certificates of GMP Compliance issued by each country's regulatory agencies and to accept batch testing certificates held by a manufacturer without re-control of that batch at import. See the press release here.

MHRA Publishes Guidance on the Role of the Access Consortium

December 10, 2020

From 1 January 2021, the MHRA will become a full member of the Access Consortium, along with the Therapeutic Goods Administration, Health Canada, Health Sciences Authority of Singapore and Swissmedic. The MHRA has published **guidance** explaining the role of the Access Consortium. The consortium is a medium-sized coalition of regulatory authorities that work together to promote greater regulatory collaboration and alignment of regulatory requirements.

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MHRA Publishes Guidance on the Access Consortium's New Active Substance (NAS) Work Sharing Initiative

December 10, 2020

The **guidance** explains that the Access Consortium's New Active Substance Work Sharing Initiative has successfully approved several medicines through this international collaboration and continues to foster cooperation and strong relationships between its Access partners. By engaging in these partnerships, Access is able to co-ordinate regulatory review procedures, and increase each agency's capacity to ensure consumers have timely access to high quality, safe and effective therapeutic products. Interested applications should contact access-mhra@mhra.gov.uk using the 'Expression of Interest' form, three to six months before submission and then submit identical dossiers to the relevant authorities participating in the work sharing initiative.

MHRA Publishes Guidance on the Access Consortium's Generic Medicines Work Sharing Initiative

December 10, 2020

The MHRA has published **guidance** on the Access Consortium's Generic Medicines Work Sharing Initiative. The guidance explains that this is a work sharing model for the co-ordinated assessment of a generic application that has been filed with multiple Access Consortium agencies. Interested applicants should express interest in the initiative using the Expression of Interest (EOI) form; this should be done 3 - 6 months before the target submission date.

MHRA Publishes Guidance Explaining What the Project Orbis Initiative is and MHRA Involvement in This Regulatory Path

December 10, 2020

From 1 January, 2021 the MHRA will become a full member of Project Orbis. The MHRA has published **guidance** explaining that Project Orbis is a programme coordinated by the US FDA to review and approve promising cancer treatments. It involves the regulatory authorities of Australia, Canada, Singapore, Switzerland and Brazil. Project Orbis 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.

UK Medicines Regulator Joins Two Initiatives to Speed up the Approval of Innovative Medicines from January 1, 2021

October 14, 2020

The Department of Health and Social Care has published a **press release** titled "Cutting-edge treatments to be fast-tracked to patients through international collaborations.

The United Kingdom will be joining two initiatives that bring together some of the world's leading regulators to allow pharmaceutical companies to submit medicines to be reviewed by several countries at the same time, pooling resources and allowing patients to benefit from earlier access.

The two schemes aim to ensure that patient safety and scientific integrity are upheld to the highest possible standards, while removing red tape and working together to get medicines onto the market quicker:

- **Project Orbis:** This program reviews and approves promising cancer treatments. It is coordinated by the U.S. Food and Drug Administration, involving Canada, Australia, Switzerland, Singapore, and Brazil.
- **Access consortium:** This program helps secure improved patient access to high-quality, safe, and effective medicines. It involves Australia, Canada, Switzerland, and Singapore. Previously, the consortium has approved nine innovative prescription medicines (including five new cancer treatments).

The **key benefits** to sharing the evaluation of medicines across the group are:

- Reducing the duplication of effort, leading to more efficient and effective regulatory review
- Promoting distribution of work to facilitate regulatory decisions
- Joining efforts in learning from each other, adopting a flexible approach to application management, and using the best parts of each evaluation pathway
- Sharing the evaluation of new drug applications, which is cost-effective for the regulators
- Sharing knowledge and expertise, continually improving its regulatory practices, and sharing global regulatory intelligence
- Post-market activities that are helping to identify emerging safety concerns
- Greater access to additional regulatory experts, opportunities for technical discussions, and more informed decision-making
- Partner agencies gaining a greater understanding of areas where their regulatory frameworks diverge, which has increased the potential for better harmonization in the future
- Clear efficiencies in the development of best practice, the sharing of guidance and procedural documents, and international alignment

The MHRA will participate as an observer of both groups before the end of 2020 and will be a full participant from January 1, 2021 after the end of the transition period. The MHRA will have the authority make the final decision to authorize medicines onto the UK market and will have complete autonomy to streamline the approval processes even further if needed outside both schemes.

- **NICE**

NICE Issues a Statement Detailing Its Efforts to Prepare for the End of the Transition Period, Including Its Collaborative Efforts with the MHRA

November 19, 2020

The National Institute for Health and Care Excellence (NICE) has published a statement detailing its efforts to prepare for the end of the transition period and the new regulatory environment for medicines and medical technologies. NICE is collaborating with the MHRA to design a streamlined process for licensing and evaluating new medicines for use in the NHS from January 1, 2021. NICE plans to align its evaluation of new medicines through the Technology Appraisals and Highly Specialised Technologies processes with the MHRA licensing timelines to ensure patients in the NHS can access new medicines and products in a timely way. See the statement **here.**