Client Alert

September 2020

UK's MHRA Publishes Extensive Post-Transition Brexit Guidance

In brief

On September 1, 2020, the UK's medicines and medical devices regulator released the MHRA post-transition information, an extensive suite of guidance on the UK regulatory regime post the Transition Period expiring on December 31, 2020.

The new guidance spreads out across dozens of documents covering the following topics:

Clinical trials
Devices
Licensing
Importing and Exporting
IT systems
Pharmacovigilance
Paediatrics

Given that up to now, the industry has been left with no clarity other than the withdrawn previous No-Deal guidance, this publication is largely to be welcomed. It provides more certainty on a number of areas to and although it is largely similar to the previous guidance that was withdrawn earlier in 2020, it provides additional detail and in some cases deviates from that guidance, and so requires careful reading.

Extensive though the new guidance is, certain gaps in detail provided still remain, and we continue to follow up with the MHRA in these important areas.

We have prepared a summary of the new guidance, which can be accessed below.

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In depth/In more detail/Background

CLINICAL TRIALS (2 guidance documents issued within this topic):

1. **Registration of clinical trials for investigational medicinal products and publication of summary results from 1 January 2021**

    - From 1 January 2021, you should continue to use existing and established international registers such as ISRCTN registry (UK), or ClinicalTrials.gov (USA), to ensure the public is aware of your trial. For trials involving both UK and EU sites a record in the EU Clinical Trials Register will exist (other than adult Phase 1 studies).

    - In the UK, any favourable opinion given by a research ethics committee is subject to the condition that the clinical trial is registered on a publicly accessible database. Registration should occur before the first participant is recruited and no later than six weeks after recruitment of the first participant. You should include the link to where your study is registered in the Integrated Research Application System (IRAS) when you prepare your application.

    - If a sponsor wishes to request a deferral of study registration within the required timeframe, in accordance with current transparency rules (e.g., due to commercial sensitivity), they should contact the Health Research Authority (HRA) at study.registration@hra.nhs.uk.

    - The UK will continue to make information about trials being conducted in the UK available to the public, patients, researchers and clinicians via the HRA research summaries website and UK "Be Part of Research" website.

- **Publishing trial results**

    - The time frame for publishing the summary of results is within 6 months of the end of trial for paediatric clinical trials or within one year of the end of trial for non-paediatric clinical trials.

    - Actions for those publishing results from 1 January 2021

        1. You should publish your summary results within these timeframes in the public register (or registers) where you have registered your clinical trial.

        2. You do not need to submit this clinical trial summary report to the MHRA as well; however, you must send a short confirmatory email to CT.Submission@mhra.gov.uk once the result-related information has been uploaded to the public register and provide a link.

3. You should also submit a final report to the Health Research Authority within the same timeframe for reporting the summary of results

2. **Guidance on substantial amendments to a clinical trial from 1 January 2021**

- **Changes to the trial sponsor/legal representative**
    - The UK will require the sponsor or legal representative of a clinical trial to be in the UK or country on an approved country list which would initially include EU/European Economic Area (EEA) countries.
    - A change in sponsor or legal representative for an UK trial is a substantial amendment requiring submission to both MHRA and the Research Ethics Committee (REC).
- **Action to take from 1 January 2021**
    - Where the sponsor is from the rest of the world and the legal representative is established in the UK and there are sites elsewhere in the EU/EEA, the sponsor will need to assign an EU/EEA legal representative for these sites via a substantial amendment to the relevant EU/EEA competent authorities.
    - No amendment submission to MHRA is required where the sponsor or legal representative for an ongoing trial is established in the EU/EEA as the UK will continue to accept this.
    - No amendment will need to be submitted in the UK if the sponsor retains the UK legal representative for the UK study. Similarly, no amendment will need to be submitted in the UK if a sponsor remains in the UK and a legal representative is added to cover EU/EEA sites.
- **Investigational medicinal product (IMP) certification and importation**
    - As is the case today, a substantial amendment will be required to be submitted to MHRA to change (add/replace) any IMP manufacturing, importation or certification site relevant for supply of IMP to an ongoing UK trial.
    - If the sponsor chooses to retain an existing UK IMP release site for the ongoing UK trial but includes an additional EU/EEA site for trials in the EU/EEA only, then no substantial amendment to MHRA will be required.
    - 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 1 January 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 1 year of 1 January 2021.
    - This means that for up to 1 year after 1 January 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 relevant to the Research Ethics Committee (REC)**
    - The Health Research Authority (HRA) has produced guidance on when amendments are required to be submitted for REC review.

DEVICES (1 guidance document):

1. Regulating medical devices from 1 January 2021

- From 1 January 2021 the MHRA will take on the responsibilities for the UK medical devices market that are currently undertaken through the EU system.
- **Summary of key requirements for placing a device on the Great Britain market**
    - From 1 January 2021, there will be a number of changes to how medical devices are placed on the market in Great Britain. These are:
        - CE marking will continue to be used and recognised until 30 June 2023
        - Certificates issued by European Economic Area (EEA)-based Notified Bodies will continue to be valid for the Great Britain market until 30 June 2023
        - A new route to market and product marking will be available for manufacturers wishing to place a device on the Great Britain market from 1 January 2021
        - From 1 January 2021, all medical devices and in vitro diagnostic medical devices (IVDs) placed on the UK market will need to be registered with the MHRA. There will be a grace period for registering:
            - 4 months for Class IIIs and Class IIb implantables, and all active implantable medical devices
            - 8 months for other Class IIb and all Class IIa devices

- 12 months for Class I devices

  - The above 12-month grace period will not apply to manufacturers of Class I devices and general IVDs that are currently required to register with the MHRA.

  - If you are a manufacturer based outside the UK and wish to place a device on the UK market, you will need to establish a UK Responsible Person who will take responsibility for the product in the UK.

- **Registering your device from 1 January 2021**

  - Given that this is an extension of existing registration requirements, there will be a grace period to allow time for compliance with the new registration process.

  - For the following devices, you will have 4 months to register with the MHRA (until 30 April 2021):

    - Active implantable medical devices

    - Class III medical devices

    - Class IIb implantable medical devices

    - IVD List A

  - For the following devices, you will have 8 months to register with the MHRA (until 31 August 2021):

    - Class IIb non-implantable medical devices

    - Class IIa medical devices

    - IVD List B

    - Self-test IVDs

  - For the following devices, you will have 12 months to register with the MHRA (until 31 December 2021):

    - Class I medical devices

    - General IVDs

  - Note that the above 12-month grace period will not apply to manufacturers of Class I devices and general IVDs that are currently required to register with the MHRA.

  - Registration for custom-made devices will be in line with the risk class of the device. Failure to register by these dates will mean

that you will no longer be able to lawfully place your device on the UK market.

- Class I devices, custom-made devices and general IVDs being placed on the Northern Ireland market must continue to register as normal as the 12-month grace period will not apply.

- More information on registrations (including fees) can be found in the MHRA's registrations guidance.

LICENSING (there are 12 separate guidance documents within this topic):

1. **Conditional Marketing Authorisations, exceptional circumstances Marketing Authorisations and national scientific advice from 1 January 2021**

   - **Guidance for Great Britain Conditional Marketing Authorisation Applications**

     - The MHRA **will introduce a national Conditional Marketing Authorisation (CMA) scheme for new medicinal products in Great Britain (England, Wales and Scotland) from 1 January 2021.**

     - The scheme will have the same eligibility criteria as the EU scheme and is intended for medicinal products that fulfill an unmet medical need.

     - 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. However, MAA must still contain adequate evidence of safety and efficacy to enable the MHRA to conclude that the risk-benefit balance of the medicinal product is positive.

     - There is no specific application route for a CMA; applicants should submit their MAA dossier as for a full Marketing Authorisation.

     - CMAs will be valid for one year and will be renewable annually.

   - **Guidance for Great Britain Marketing Authorisations under exceptional circumstances**

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

   - Guidance for national scientific advice after 1 January 2021

- The MHRA will **continue to offer its national scientific advice service after 1 January 2021**.

- This service is available for developers of medicinal products and can be requested at any stage of the product's development.

- From 1 January 2021 there will be **one change to the fees payable** for scientific advice and applications for scientific advice submitted by UK-based Small and Medium-sized Enterprises (SME) will be exempt from the fee.

2. Registering new packaging information for medicines from 1 January 2021

- Once you have been issued with your new Marketing Authorisation (MA) to convert a previously EU-wide to an MA for Great Britain, you will have no later than 24 months after the end of the transition period to establish and register a Great Britain presence for your MA.

- You will have a further 12 months (36 months in total from 1 January 2021) to ensure all stock released to market is in compliant packaging. This additional time allows for assessment of your submission(s) and time for implementation in the production schedule.

- You may need to amend the labelling and/or the patient information leaflet (PIL) to take account of new information as a result of a variation application submitted between the grant of the new MA and 24 months from 1 January 2021.

- In such cases, the changed artwork which accompanies that variation application should include the new administrative information at that earlier time.

- **National MAs granted after a mutual recognition or decentralised procedure**

  - MAs previously the subject of a mutual recognition or decentralised submission will be considered as purely national licences. 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.

- **Submission and best practice**

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

3. Guidance on the handling of applications for Centrally Authorised Products (CAPs) pending on 1 January 2021

- Currently pending and future applications for Community Marketing Authorisations will continue to include Northern Ireland, and when

granted the authorisation will cover marketing of the product in Northern Ireland.

- The guidance sets out how the MHRA, acting for Great Britain, will handle centralised applications that are still pending on 1 January 2021. The handling will be determined by the regulatory route chosen by the company and the stage of the procedure the application was at on that day.

- To summarise, the company has two options:

    - To apply to MHRA for an in-flight assessment of a Great Britain MA in parallel with the application for an EU MA. In that case the approach of the MHRA will be to take into account any assessment that has already been reported on/before 1 January 2021 with a view to completing the application no later than the issue of the EU Commission Decision.

    - To wait for the Commission for Medicinal Products for Human Use (CHMP) positive opinion and to apply to Great Britain using the new Reliance Route as explained in published guidance on new application routes to market. The application will be determined when the EC decision has been confirmed.

- In all cases, as the MHRA does not hold supporting data for applications made to the EMA, applicants will need to submit an application and supporting dossier to the MHRA accompanied by all iterations of the CHMP assessment report.

- The handling of applications at all stages of the EU procedure is summarised in this table.

4. How Marketing Authorisation Applications referred under Article 29 will be handled from 1 January 2021

- For MAAs that have been referred under Article 29, where either a positive or negative opinion has been taken at the Coordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh) or the Committee for Medicinal Products for Human Use (CHMP) but no decision issued by 1 January 2021, the MHRA will either grant or refuse the application with regard to the relevant committee decision.

- For all pending MAAs submitted in the UK, as a Concerned Member State (CMS), that have been referred under Article 29 before 1 January 2021 but no opinion has been reached by CMDh or CHMP, the MHRA will complete the assessment for Great Britain as a national procedure.

- The MHRA assessment will take into account the existing RMS and CMS assessments with particular focus on the identified PSRPH. If the MHRA are minded to refuse an application based on a PSRPH, consultation with the Commission on Human Medicines (CHM) and other relevant expert advisory committees will take place.

- On completion of the MHRA assessment, and consultation with expert advisory committees as required, the MHRA will issue its decision on approval or refusal of the Marketing Authorisation.

5. Converting Parallel Distribution Notices (PDNs) to UK Parallel Import Licences (PILs) from 1 January 2021

- At the end of the transition period, the UK will have in place arrangements for the continued authorisation of medicinal products.
- **Great Britain**
    - Parallel Distribution Notices will no longer be valid in Great Britain (England, Scotland, Wales) and will be replaced by Parallel Import Licences which will allow the products to be marketed in Great Britain only.
    - PDN holders are given the opportunity to opt-in to the conversion process for all or some of their PDNs by notifying the MHRA in writing. *This compares to the old guidance which stipulates that holders of parallel distribution notices, issued by the EMA, in respect of CAPs will, where the UK is listed in that notice as a destination country, be automatically, and with no fee, issued with a parallel import licence, subject to providing specified information on the products to be imported to the MHRA by 21 February 2020*.
    - Under the new guidance, if you choose not to opt-in, following the end of the transition period your product(s) will no longer be licensed in Great Britain and you will no longer be able to place them on the market in Great Britain.
    - MHRA will allocate Product Licence (PL) numbers to PDNs based on the existing practice for determining how many separate national licences are needed across a product range. All pack sizes will be covered by a single PL number.
    - PILs will be valid for a single source country and a separate PIL will be issued for each source country you request.
    - There is no fee associated with the conversion from a PDN to a Great Britain PIL. However, a periodic fee of £307 will be due on 1 April 2021 for each PIL requested unless a request to cancel the PIL on 31 March 2021 has been notified to MHRA (plpi@mhra.gov.uk) no later than 31 December 2020.
- **Northern Ireland**
    - Parallel Distribution Notices will remain valid in Northern Ireland and no regulatory action is required to continue to market products directly imported from EU into Northern Ireland only.

6. **Handling of Active Substance Master Files and Certificates of Suitability from 1 January 2021**

- From 1 January 2021, the MHRA will continue to accept an Active Substance Master File and/or a Certificate of Suitability in both new national initial Marketing Authorisation Applications (MAA) and in Marketing Authorisation Variation (MAV) applications.

- The UK will no longer participate in ASMF worksharing procedures with EU Member States.

- Any reference in the above guideline to the CTS ASMF assessment repository or to EU/ASMF/XXXXX reference numbers will not be applicable to UK national applications from 1 January 2021.

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

- Certificates of Suitability (CEPs) are not affected by the UK leaving the EU as they are issued by the European Directorate for the Quality of Medicines and Healthcare (EDQM). This is a Directorate of the Council of Europe and a body that is independent of the EU. On leaving the EU, the UK will remain a member of the Council of Europe and a signatory to the Convention on the Elaboration of a European Pharmacopoeia.

- There will be no change to the procedures relating to the use of a CEP to support an MAA or MAV.

7. **Reference Medicinal Products (RMPs) from 1 January 2021 Great Britain (England, Wales and Scotland): Reference Medicinal Product (RMP)**

- From 1 January 2021 reference medicinal products for new generic medicines or other abridged marketing authorisation applications submitted after 1 January 2021 will have to fall within the definition in regulation 48 of the Human Medicines Regulations 2012, as amended by the Human Medicines (Amendment etc.) (EU Exit) Regulations 2019.

- The MHRA intends to update these Regulations to reflect the change of implementation dates following the Transition Period.

- These regulations will include:

    - products that are, or have been, authorised for at least 8 years in the UK (including those authorised by conversion from EU marketing authorisations)

    - products that had an EU marketing authorisation on 1 January 2021 but which did not convert into Great Britain marketing authorisations as the holder opted out of that process.

- Data and market exclusivity period entitlements for reference medicinal products approved before 1 January 2021 will continue to apply in the UK.

- Authorisations based on a 'European Reference Medicinal Product' that have been granted, and applications that have been submitted to MHRA prior to 1 January 2021, will continue to be valid.

- For applications submitted to MHRA from 1 January 2021, The RMP will need to fall within the definition in regulation 48 of the Human Medicines Regulations 2012, as amended by the Human Medicines (Amendment etc.) (EU Exit) Regulations 2019. It is the MHRA's intention to update these Regulations to reflect the change of implementation dates following the Transition Period.

Non-UK comparator products

- Where a comparator product used in bioequivalence and therapeutic equivalence studies is not sourced from the UK market, the applicant should provide evidence that it is representative of the reference medicinal product.

- This guidance will apply from 1 January 2021 in line with the Human Medicines Regulations (Amendment etc.) (EU Exit) Regulations 2019. It is the MHRA's intention to update these Regulations to reflect the change of implementation dates following the Transition Period.

Northern Ireland

- The EU medicines legislation will remain applicable in Northern Ireland. Reference medicinal products 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 Human Medicines Regulations 2012, as amended by the Human Medicines (Amendment etc.) (EU Exit) Regulations 2019 includes UK authorised products and products in relation to which there is an EU marketing authorisation, or 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.

8. Converting Centrally Authorised Products (CAPs) to UK Marketing Authorisations (MAs) from 1 January 2021, 'grandfathering' and managing lifecycle changes

- **General approach to grandfathering of CAPs**

    - All existing CAP MAs will automatically be converted into UK MAs effective in Great Britain (only) and issued with a UK MA number on 1 January 2021. ("converted EU Mas")

- To opt out of the conversion process you must let the MHRA know by the end of 21 January 2021.
- The MHRA will issue one or more Product Licence (PL) numbers to CAPs based on the existing UK practice for determining how many separate national licences are needed across a product range.
- There is no fee associated with the conversion from a CAP to a Great Britain MA.
- If the MAH chooses to opt-out, their product(s) will no longer be licensed and must not be marketed in Great Britain.
- MAHs will have a period of one year starting on 1 January 2021 to submit this data and related information in eCTD format.

- **Actions that holders of converted EU MAs need to take**
  - Within the period of one year starting on 1 January 2021, the MAH must submit:
    - cover letter and declaration that only approved documentation is included in the initiating sequence.
    - a single eCTD initiating sequence for the converted EU MA representing the currently authorised and approved position
    - a completed electronic application form (eAF) for each converted EU MA.
    - a summary list of all historical regulatory activity from the grant date of the original CAP until the data is submitted.
    - notification of whether or not the product referred to in the converted EU MA is on the Great Britain market at the time the notification is given. If it is not, the MAH must state whether the product has been on the Great Britain market at any time after 1 January 2021 and, if so, the date it was withdrawn from the market.
    - the Summary of Product Characteristics (SmPC) currently approved by corresponding EU procedure
    - the packaging labels and leaflets as currently approved by the corresponding EU procedure

- How to submit the application
  - MHRA have developed a new national portal to be ready by 1 January 2021 and expect that submissions will be made via this portal, and not the Common European Submission Portal (CESP)

- Specific advice on preparing the initiating sequence
    - Background information on the latest version of the eCTD standard, including EU guidance on Module 1 information and the electronic application form can be found on the EMA e-submissions website.
- Submitting the initiating sequence in two steps
    - In certain circumstances the MAH can use a two-step process by first submitting a minimal initiating sequence containing at least the mandatory documents at an early point following 1 January 2021.
    - All a further complete initiating sequence, containing all documents electronically must be submitted within a period of one year starting on 1 January 2021
- General approach to variations to converted EU MAs from 1 January 2021
    - In general, the MHRA will not consider variations to converted EU MAs before at least a minimal initiating sequence and related documentation have been submitted, unless there are exceptional circumstances
    - For the purpose of renewals, converted EU MAs are treated as if they were granted on the date on which the corresponding EU MA was granted.
    - MHRA may consider a renewal before the data submission date under exceptional circumstances
- Approach to variations submitted to the EMA but not granted before 1 January 2021
    - *See* summary *table at the bottom*
- Approach to variations to converted EU MAs applied for from 1 January 2021
    - *See summary table at the bottom*
- General approach to renewals to converted EU MAs from 1 January 2021
    - For the purpose of renewals, converted EU MAs are treated as if they were granted on the date on which the corresponding EU MA was granted.
    - In general, the MHRA will not consider renewals to converted EU MAs before at least a minimal initiating sequence and related documentation has been received.

- In exceptional circumstances, MHRA may consider a renewal before the data submission date

- Approach to variations submitted to the EMA but not granted before 1 January 2021. Application guidance are provided on the following:

Converted EU MAs

- the CHMP has given a positive final opinion and the UK concurred, the renewal will be treated as accepted

- the renewal had not reached CHMP opinion and was in clock-stop following a request for further information

- the renewal had not reached CHMP opinion and was before clock stop

- the CHMP had given a negative final opinion or had given a positive final opinion but the UK had recorded a divergent opinion, the renewal will be considered in line with normal MHRA practice

Converted Conditional EU MAs

- where, before 1 January 2021, the CHMP had given a positive final opinion and the UK concurred, the renewal will be treated as accepted

- where, before 1 January 2021, the CHMP had not given an opinion or had given a negative final opinion or had given a positive final opinion but the UK recorded a divergent opinion, the renewal will be reviewed by the MHRA

- Approach to variations to converted EU MAs applied for from 1 January 2021

  - the MAH must submit an application for renewal and the application should be submitted as a separate eCTD sequence along with the initiating sequence if this has not already been submitted. The renewal will only be considered after the baseline is processed.

    - for Converted EU MAs, the application should be accompanied by the appropriate fee

    - for Converted Conditional EU MAs, no fee is due and the application will be considered under the new regulatory 66B

- General approach to Article 61(3) notifications for converted EU MAs from 1 January 2021

  - In general, the MHRA will not consider Article 61(3) notifications for converted EU MAs before at least a minimal initiating

sequence and related documentation has been received, unless there are exceptional circumstances

- Approach to Article 61(3) notifications submitted to the MA but not granted before 1 January 2021. Application guidance is provided where:
    - the holder of a converted EU MA has made an Article 61(3) notification for the corresponding EU MA before 1 January 2021,
    - the change is applicable to the product information intended for the UK market,
    - the 90-day period referred to in Article 61(3) has not elapsed,
    - the EMA has not objected to the change.
- Approach to Article 61(3) notifications made from 1 January 2021
    - Where the holder of a converted EU MA has made an Article 61(3) notification for the EU MA from 1 January 2021 but before the data submission date, and the change is applicable to the product information intended for the Great Britain market, the notification must be included within the initiating sequence submission as if it had already been accepted in Great Britain.
    - The change may be put in effect at the same time as for the EU MA.
    - No fee will apply for these notifications.
- Legal presence requirement
    - For grandfathered CAP MAs with a non-UK MAH, there is a requirement to establish an MAH in the UK within 24 months of 1 January 2021 (by 1 January 2023). MAHs have two options:
        - Submit a Change of Ownership application (COA) after the submission of the baseline initiating sequence within 21 months after the transition period
        - Include the COA in the initiating sequence as if it had already been approved by the MHRA and state in the cover letter that this option had been adopted.
- **Summary of approach to variations**

Variation	**Positive CHMP Opinion Stage before exit day**	**MHRA assessment**	**Fee payable**	**Include in Initiating Sequence**

Type IA: (i) Submitted to EMA before 1 January 2021 and not rejected or, (ii) submitted to EMA on or after 1 January 2021 and not rejected before data submission date	N/A	No	No	Yes, (and list in summary of historical regulatory activity accompanying Initiating Sequence)
Type IB: Submitted to EMA but not granted before 1 January 2021	Yes	No	No	Yes, (and list in summary of historical regulatory activity accompanying Initiating Sequence)
Type IB: Submitted to EMA but not granted before 1 January 2021	No	No	No	Yes, (and list in summary of historical regulatory activity accompanying Initiating Sequence)
Type II: Submitted to EMA but not granted before 1 January 2021	Yes	No	No	Yes, (and list in summary of historical regulatory activity accompanying Initiating Sequence)
Type II in clock stop: Submitted to EMA but not granted before 1 January 2021, And in clock stop	No	Yes, assessment of replies	No	No: Separate Submission needed along with or after Initiating Sequence (either minimal or complete)
Type II in clock stop: Submitted to EMA but not granted before 1 January 2021, And	No	Yes	Yes	No: Separate Submission needed along with or after Initiating Sequence

before procedure first clock stop				(either minimal or complete)
Type IB/II variations: Submitted to EMA on or after 1 January 2021	N/A	Yes	Yes	No: Separate Submission needed along with or after Initiating Sequence (either minimal or complete)

9. Renewing Marketing Authorisations for medicines from 1 January 2021

- CAPS converted from EU to UK MAs will be treated as if they were granted on the same date as the corresponding EU MA and the renewal date will be the same (please see detailed advice for CAPS above).

- Renewals submitted for MAs granted through mutual recognition or decentralised procedures:

    - Where a request for a renewal does not receive a decision before 1 January 2021, a new one will not need to be resubmitted.

    - Where a final decision has been made but it hasn't been processed before 1 January 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 appropriately.

- If renewing from 1 January 2021, the requirements for renewal submissions remain the same and renewal applications should continue to be submitted 9 months before they expire. For conditional MAs, renewal applications should be submitted to the MHRA 6 months before they expire.

- New fees will be £9,682 for first renewal of a product containing a new active ingredient at the time of authorisation and £747 for related applications made at the same time as the first renewal. There will be no fees for subsequent MA renewal applications or for renewing conditional MAs. *This compares to the old guidance which stipulates that all new active substances were subject to a single renewal fee of £9,682 for the five year renewal application from when the licence was first granted*.

10. **Guidance on new provisions for traditional herbal medicinal products and homoeopathic medicinal products from 1 January 2021**

- **Traditional Herbal Medicines**
    - Currently, evidence has to be provided that the herbal medicine product or a corresponding product has been used for a period of 15 years within the EU/EEA but from 1 January 2021, the MHRA may be able to accept the 15 years of traditional evidence from a wider range of countries than just those in the EU.
    - The countries will be those which have a level of pharmacovigilance equivalent to that of the UK.
    - The provision will not apply to traditional herbal medicines to be marketed in Northern Ireland which will maintain the current status quo.
    - 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 (but only the EU list will be relevant to Northern Ireland).
- **Homeopathic medicines**
    - The definition of homeopathic medicinal product will be expanded from 1 January 2021 to cover products from homeopathic stocks made in accordance with a homeopathic manufacturing procedure (as described in the European Pharmacopoeia, British Pharmacopoeia or Pharmacopoeia used officially in an EEA country).
    - Provision will not apply to products marketed in Northern Ireland and the current EU definition will remain in Northern Ireland.

11. **Guidance on licensing biosimilars, ATMPs and PMFs from 1 January 2021**

- **Great Britain (Eng, Wales and Scotland) MA applications for similar biological products (biosimilars)**
    - From 1 January 2021, the MHRA will regulate biosimilar products in the same way they are regulated now; Northern Ireland will follow the EU acquis and the MHRA will regulate accordingly
    - New applications should be submitted using existing procedures for national levels
    - For biosimilar applications submitted after 1 January 2021, the application must be made with reference to a product that falls within the definition of reference medical products (regulation 48

of the Human Medicines Regulations 2012), as amended by Human Medicines (Amendment etc.) (EU Exit) Regulations 2019.

  - These will be products which have been authorised for at least 8 years (either in the UK or by conversion from EU MAs); products which had an EU MA in force on 31 December 2020 but which did not convert into GB MA; and products for which EU MA has ceased to be in force for reasons not related to safety, quality or efficacity.

- Data and market exclusivity period entitlements for reference medicinal products approved before the date of UK exit will continue to be applicable.

- GB will continue to accept data generated on reference product sourced in accordance with the 'Guideline on similar biological medicinal products CHMP/437/04 Rev1'.

- **GB MA applications for Advanced Therapy Medicinal Products (ATMPs)**

  - From 1 January 2021, ATMPS will be regulated nationally in relation to GB by the MHRA in the way they are regulated now; Northern Ireland will continue to be regulated according to EMA's Centrally Authorised Procedure.

  - Data, traceability, exemptions from licensing, packaging and post-authorisation requirements will remain unchanged, as will definitions of individual classes of ATMPs.

    - Classification on ATMPs in the UK will be undertaken by the MHRA in accordance with legislation and current guidance

    - They will continue to be classified into either: gene therapy medicinal products, somatic cell therapy medicinal products or tissue engineered products.

    - If uncertain about the classification of your products, fill out the ATMP advice form or consult the Reflection paper on classification of advanced therapy medicinal products (EMA/CAT/600280/2010 rev.1).

- **Guidance for Plasma Master Files (PMFs) an Vaccine Antigen Master Files (VAMFs)**

  - From 1 January 2021, the MHRA will continue to recognise the existing PMF and associated inspections until further notice (although the supervision of the PMFs may eventually be transferred into a national system, details of which will be communicated by the MHRA at a later date).

  - In the meantime, PMF holder is required to notify the MHRA of the outcome of annual updates within 4 weeks of the completion

of the update, and for variation applications submitted to the EMA, PMF holder must notify of submission and determination outcome within 4 weeks of the submission and determination dates, respectively.

    - MHRA reserves the right for further review where an EU assessment report indicates significant public health issues that are insufficiently address at European level.

- MHRA will issue guidance on the transfer of OMFs to the MHRA database when this becomes relevant - data requirements will be in accordance with those currently in place in the EU.

- No VAMF is in use in the UK at present so applicants proposing a submission should contact the MHRA for further guidance.

12. Comparator products in Bioequivalence/Therapeutic Equivalence studies from 1 January 2021

- (limited to applications intended for the Great Britain (England, Wales and Scotland) market only. Applications intended for Northern Ireland will be required to comply with EU requirements for comparator products to be used in studies.)

- From 1 January 2021, reference medicinal products (RMP) for new generic medicines or other abridged marketing authorisation applications submitted from this date will be required to comply with the relevant legislation.

- **Comparator products used in bioequivalence and therapeutic equivalence studies**

    - Comparator products (CPs) used in bioequivalence (BE), pharmacokinetic (PK) and therapeutic equivalence (TE) studies supporting abridged applications should be representative of the RMP supporting the application.

    - Generally, the CP should be sourced from Great Britain (England, Wales and Scotland). However, if the CP is not sourced from the Great Britain market, the applicant should provide evidence that it is representative of the RMP.

    - With the aim of facilitating the global development of medicinal products and to avoid unnecessary repetition of clinical BE/TE studies, it may be possible for an applicant to compare the proposed medicinal product with a non-Great Britain sourced CP. The application for the new medicinal product would still be required to refer to an eligible RMP.

    - It will be the applicant's responsibility to demonstrate that any CP authorised and sourced from outside the UK is representative of 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.

- 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 3 products.

- 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.

IMPORTING AND EXPORTING (6 guidance documents):

1. **Importing medicines on an approved country for import list from 1 January 2021**

   - **Importing medicines from an EEA State which is on an approved country for import list**

     - If you hold a wholesale dealer's licence it will remain in force from 1 January 2021

   - **Actions to take so your licence can permit the importation of medicinal products from a country which is on an approved country for import list**

     - This licence will also permit the importation of medicinal products from a country which is on an approved country for import list (initially, this will be countries in the European Economic Area (EEA)) if you undertook this activity before 1 January 2021 and take the following actions:

       - within 6 months from 1 January 2021, notify MHRA in writing of your intention to continue to import medicinal products from a country on the list

       - within 2 years from 1 January 2021, nominate and have named on your wholesale dealer's licence a Responsible Person (import) (RPi) who will carry out specific functions

     - You do not need an RPi if the medicine imported from the listed country is not licenced in the UK or the listed country and the medicinal product is either for use as a special medicinal product

or is to be exported by the importer as an introduced medicine. This is because of an exemption in relation to the need for a RPi.

- In this case you must within 6 months from 1 January 2021, notify MHRA in writing of your intention to only import medicinal products from the listed country, to which this exemption applies.

- If you do not hold a wholesale dealer's licence before 1 January 2021, in order to wholesale deal medicine you will need to apply for a wholesale dealer's licence. The requirement to name a RPi on the wholesale dealer's licence will apply immediately to all new licence applications made from 1 January 2021 if you wish to import a licensed medicine from a listed country.

- **Importing UK or Great Britain authorised human medicines from a country on the list for use in Great Britain**

- If you import a UK or Great Britain (England, Wales and Scotland) authorised medicine from a country on the list, you will need to hold a wholesale dealer's licence that authorises import.

- This licence will need to cover the following activities of handling medicinal products:

  - With "an authorisation" (a UK or Great Britain Marketing Authorisation, certificate of registration or traditional herbal registration)

  - Your licence must authorise wholesale distribution operations, including:

    - Products imported from countries on a list,

    - Products certified under Article 51 of Directive 2001/83/EC.

- **Importing human medicines from a country on the list for use as a special medicinal product**

  - If you import a medicine from a country on the list, for use as a special medicinal product in Great Britain, you will need to hold a wholesale dealer's licence that authorises import.

- **Importing medicines licensed in the listed country**

  - If the medicine is licensed in the listed country, you will need a RPi.

  - Your wholesale dealer's licence will need to cover the following activities of handling medicinal products:

    - Without "an authorisation" (a UK or Great Britain Marketing Authorisation, certificate of registration or traditional herbal

registration) in Great Britain and intended for the Great Britain market.

- This licence will also need to authorise wholesale distribution operations covering:
  - Products imported from countries on a list
  - Products certified under Article 51 of Directive 2001/83/EC
- The current notification of intent to import an unlicensed medicine remains the same.

- **Importing medicines not licensed in the listed country**
- If the medicine is not licensed in the UK or a listed country, you will need an ordinary Responsible Person and not a RPI.
- Your wholesale dealer's licence will need to cover the following activities of handling medicinal products.
  - Without "an authorisation" (a UK or GB Marketing Authorisation, certificate of registration or traditional herbal registration) in Great Britain and intended for the Great Britain market
- Your licence will also need to authorise wholesale distribution operations covering:
  - Products imported from countries on a list
  - Products not certified under Article 51 of Directive 2001/83/EC
- The current notification of intent to import an unlicensed medicine remains the same.
- **Importing human medicines from a country on the list for export as an introduced medicine**
- If you import a medicine into Great Britain from a country on the list, that you will export as an introduced medicinal product, you will need to hold a wholesale dealer's licence that authorises import and export.
- **Importing medicines licensed in the listed country as an introduced medicine**
- If the medicine is licensed in the UK or a listed country, you will need a Responsible Person (import).
- Your wholesale dealer's licence will need to cover the following activities of handling medicinal products:
  - Without "an authorisation" (a UK or Great Britain Marketing Authorisation, certificate of registration or traditional herbal

registration) in Great Britain and intended for the Great Britain market

- Your licence will also need to authorise wholesale distribution operations covering:
    - Products imported from countries on a list,
    - Products certified under Article 51 of Directive 2001/83/EC
- **Importing medicines not licensed in the listed country or the UK for export as an introduced medicine**
- If the medicine is not the subject of a marketing authorisation in the UK or a listed country then you will need an ordinary Responsible Person and not an RPi to import it into Great Britain for export outside the UK.
- Your wholesale dealer's licence will need to cover the following activities of handling medicinal products:
    - Without "an authorisation" (a UK or Great Britain Marketing Authorisation, certificate of registration or traditional herbal registration) in Great Britain and intended for the Great Britain market.
- Your licence will also need to authorise wholesale distribution operations covering:
    - Products imported from countries on a list,
    - Products not certified under Article 51 of Directive 2001/83/EC.
- **Importing medicines from a country on the list for supply to the Great Britain Parallel Import market**
- If you import a medicine from a country on the list, for supply to the Great Britain Parallel Import market you will need to hold a wholesale dealer's licence that authorises import.
- The imported medicine must have the appropriate marketing authorisation in a country on the list for the designed Great Britain PLPI.
- Your licence will need to cover the following activities of handling medicinal products:
    - With a Marketing Authorisation in EEA member state(s) and intended for the UK parallel import market
- Your licence will also need to authorise wholesale distribution operations covering:
    - Products imported from countries on a list

- Products certified under Article 51 of Directive 2001/83/EC

- You will need an RPi if located in Great Britain.

- **Sourcing a medicine from Northern Ireland to Great Britain**

- If you source a medicine without an authorisation in UK or Great Britain from Northern Ireland for supply to the Great Britain market you need a wholesale dealers licence.

- The current notification of intent to import an unlicensed medicine remains the same. You will need an ordinary Responsible Person and not an RPi.

- If you source a medicine with a marketing authorisation from Northern Ireland for supply to the Great Britain Parallel Import market or for export to a third country you will need a wholesale dealers licence. You will need an ordinary Responsible Person and not a RPi.

2. **Exporting active substances manufactured in Great Britain for use in EEA and Northern Ireland from 1 January 2021**

- From 1 January 2021 we will continue to accept importation of active substances into Great Britain (England, Wales and Scotland) without a Written Confirmation from the same list of countries as currently (European Economic Area (EEA) countries, USA, Japan, Republic of Korea, Brazil, Australia, Israel and Switzerland) as well as from Northern Ireland.

- Northern Ireland will also continue to align with all relevant EU rules relating to the placing on the market of manufactured goods.

3. **Importing investigational medicinal products into Great Britain from approved countries from 1 January 2021**

- The requirements and procedures for clinical trials in the UK are set out in the Medicines for Human Use (Clinical Trials) Regulations 2004.

- Import of IMPs from an approved country:

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

  - This 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.

- A Sponsor may perform verification of QP certification in a listed country themselves if they are the holder of a UK MIA(IMP). Alternatively, they may outsource this verification to a third party who holds a UK MIA(IMP).
- There will be a one-year transition period from 1 January 2021 to implement this guidance.

- 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:
    - direct to the Great Britain clinical trial site
    - via a Great Britain storage and distribution 'hub'.
- Supply of IMP to a Great Britain clinical trial site
  - Until the QP named on the UK MIA(IMP)confirms that the batch of IMP has been appropriately certified by the listed country QP, the IMP should not be made available for use by the Great Britain trial sites.
- Using Great Britain storage and distribution 'hub'
  - You may use a distribution facility to store IMPs imported from a listed country before supply to Great Britain clinical trial sites.
- Reference and retention samples
  - Additional reference and retention samples are not specifically required to be stored within Great Britain, but the storage location should be visible to the QP named on the UK MIA(IMP)and defined in the written agreement with the Sponsor.
  - Provision for timely access to the samples by the UK competent authority should be made within the relevant written agreements.
- Importing non-investigational medicinal products for use in a clinical trial
  - Importation from a listed country should use a wholesale dealer's licence (WDA(H)). A Responsible Person for import (RPi) may be required.

4. List of approved countries for authorised human medicines from 1 January 2021

- From 1 January 2021, the Human Medicines Regulations 2012 will refer to lists of approved countries for:

- importation of medicines under a wholesale dealer's licence ("approved country for import list")
- batch testing of medicines ("approved country for batch testing list")
- manufacturing of active substances with regulatory standards equivalent to the UK ("approved country for active substances list")

- From 1 January 2021, the UK will accept batch testing (quality control testing), certification by a Qualified Person and Active Substance manufacture from countries specified in these lists.
- These lists will be reviewed at least every 3 years (but no earlier than 2 years after exit day in the case of EEA States on those lists).

5. Acting as a Responsible Person (import) from 1 January 2021

- From 1 January 2021, 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.
- This guidance describes how you can apply to be a RPi, and how to verify that QP certification of a medicine has been done in the EEA.
- RPi applications may be submitted through the MHRA Portal from 1 January 2021.
- The RPi is required to implement a system for confirming QP certification 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
- 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.
- Working as RPi and eligibility

- Have a combination of relevant qualifications and experience (guidance gives further details on this)
- It is also expected that you will be a member of a professional body with a published code of conduct.
- 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 a RPi.
- RPi applications may be submitted through the MHRA Portal from 1 January 2021.

6. **Applying for a Certificate of Pharmaceutical Product from 1 January 2021**

- The way to apply for a Certificate of Pharmaceutical Product (CPP) will not change from 1 January 2021.
- There will be an extra step in the process if to apply for a CPP for something that's currently a centrally authorised product (CAP)
  - You'll need to submit data about the product you're applying for at least 2 days before you make your CPP application.
  - You must also email exports@mhra.gov.uk to let them know when you're about to make your first CPP application. You only need to do this once.

IT SYSTEMS (1 guidance document + link to webinars):

1. **Registering to make submissions to the MHRA from 1 January 2021**

- The MHRA is making preparations to ensure that you can continue to submit regulatory and notification information to the UK.
- For applications that you plan to submit to the UK (for example, a Marketing Authorisation for the UK market), you will need to submit the information through their national portals.
- The following groups will need to ensure they follow the steps to gain access to MHRA Submissions, so they can make submissions from 1 January 2021:
  - all pharmaceutical companies involved in making medicines, regulatory submissions and vigilance activities
  - all medicines clinical trial sponsors wishing to make clinical trial submissions (Initial Applications, Substantial Amendments, End of Trial Notifications and Developmental Safety Update Reports (DSURs)) to the Agency
  - e-cigarette producers

- brokers of medicinal products

- Three short video demos cover all aspects of the user access management process - these steps will enable organisations to gain access and manage user permissions for using MHRA Submissions. You can access all three videos on Sharefile.

  - Video 1: User registration – the end to end process for adding an initial company administrator

  - Video 2: Add a new user – how to add an internal colleague as a user or company administrator

  - Video 3: Add a new external user – how to add a third party consultant/consultancy as a user or company administrator

- There are also two user reference guides which contain step by step guidance on the processes:

  - User Reference Guide – Gaining Access to MHRA Submissions

  - User Reference Guide – Managing users on MHRA Submissions

Registering to use the vigilance systems: MHRA Gateway and ICSR Submissions (relevant to all pharmaceutical companies involved in the submission of ICSRs or SUSARs to the MHRA).

- The following two short video demos cover the MHRA Gateway registration process and ICSR Submissions registration process. These steps will enable organisations to register to send and receive ICSRs/SUSARs via the MHRA Gateway or ICSR Submissions.

  - MHRA Gateway registration – the end to end process for registering to use the MHRA Gateway

  - ICSR Submissions – the end to end process for registering to use the ICSR Submissions portal

- There are two user reference guides which contain step by step guidance on the processes:

- **Registration for ICSR Submissions**

  - If you do not have the capability to send or receive via the MHRA Gateway, you can send ICSRs or SUSARs to the MHRA via **ICSR Submissions**.

  - To register for ICSR Submissions, you should visit the **ICSR Submissions**, portal select the 'Request company account' option, and follow the process outlined in the user reference guide. On receipt of your registration request, the MHRA will aim

to complete your registration within 5 working days. If you submit ICSRs or SUSARs to the MHRA via **ICSR Submissions**, you will also receive serious and non-serious UK reports from the MHRA via **ICSR Submissions**.

- **Registration for MHRA Gateway**
    - Once you have completed registration for MHRA Submissions, MHRA Submissions company administrators can register to send both ICSRs or SUSARs via the MHRA Gateway by selecting the 'Gateway Management' tile of MHRA Submissions and following the process in the user reference guide.
    - On receipt of your registration request, the MHRA will aim to complete your registration within 5 working days.
    - Once registration is completed, you are encouraged to perform a connectivity test in UAT. You will be able to confirm success via MDN receipt.
    - On sending ICSRS/SUSARs via the MHRA Gateway, you will receive an acknowledgement within 48 hours.
    - If you submit ICSRs or SUSARs to the MHRA via the MHRA Gateway, you will also receive serious and non-serious UK reports from the MHRA via the MHRA Gateway.
- From 1 January 2021 Marketing Authorisation Holders (MAHs) will be required to submit ICSRs to the UK directly, using the systems described above.
- Under current reporting modalities, the European Medicines Agency (EMA) forwards UK ICSRs (individual case safety reports) to the MHRA at the time that they are processed through the EudraVigilance system.
- As such Marketing Authorisation Holders should plan on the basis that all ICSRs that they have sent to the EMA and are processed before 11 pm on 31 December 2020 will be passed to the MHRA. Cases not processed prior to that point should be submitted via the new MHRA systems.

2. **Webinars are available for companies preparing to make submissions to the MHRA from 1 January 2021. Available here.**

PHARMACOVIGILANCE (2 guidance documents):

1. **Guidance on pharmacovigilance procedures from 1 January 2021**
    - **General Approach to the operation of pharmacovigilance**
        - MHRA will retain responsibility for Pharmacovigilance across the UK from 1 January 2021

- There will be some different requirements for products placed on the market in Great Britain (England, Wales and Scotland) vs in Northern Ireland. Products placed in the latter will need to be in line with EU legislation and follow EU requirements.

- From 1 January 2021, for medicines authorised in GB any Marketing Authorisation Holder (MAH) will need to submit pharmacovigilance data to the MHRA, according to GB requirements, including:

  - UK and non-UK Individual Case Safety Reports (ICSRs)

  - Periodic Safety Update Reports (PSURs)

  - Risk Management Plans (RMPs)

  - Post-Authorisation Safety Studies (PASS) protocols and final study reports

- The Good Vigilance Practices (GVP) modules will remain in force but a guidance note on the exceptions and modifications to the EU guidance will be published in due course

- For medicines authorised to be sold or supplied in Northern Ireland information will need to be submitted according to EU requirements; for medicines which are the subject of a UK MA covering both GB and Northern Ireland, information will need to be submitted in accordance with requirements for both GB and EU, as appropriate.

- Further guidance on the conversion of Centrally Authorised Products (CAPs) to UK MAs is available.

  - Any conditions or restrictions subject to which the CAP was granted before 1 January 2021 will apply to the converted MA, as will any post-authorisation obligations prior to that date.

- In general, submission of historical is not required but the MHRA may request it where needed for assessment purposes. Where a request is made, the data must be supplied to us within the specified time period.

- **Actions for submitting and receiving ICSRs**

  - All submissions of UK ICSRs (serious and non-serious) and serious ICSRs from other countries must be submitted via the new MHRA Gateway or ICSR Submissions portal.

  - You can register on the MHRA-Gateway and/or ICSR Submissions portal prior to 1 January 2021 to enable configuration for your system - registration should be made as early as possible.

- For products placed on the market in Northern Ireland you will need to submit ICSRs according to EU requirements to the Eudravigilance database.

- **Signal detection**

  - Signal detection systems will need to enable you to meet your requirements for cumulative signal detection across all available data sources.

  - MHRA will not require you to conduct signal detection against our own database, as we will make relevant UK data available for inclusion in your systems.

  - You are obliged to notify the MHRA of signals arising from any data source if you haven't done so already. From 1 January 2021 this also includes standalone signal notifications submitted to you by the EMA that are relevant to your products, as well as signals raised by the EMA.

  - For products placed on the Northern Ireland market, you are additionally required to report to the EMA any safety signals that are considered to meet the definition of an emerging safety issue (see GVP-Module IX Signal Management)

  - From 1 January 2021, the MHRA will carry out assessment of signals and issue decisions for both signals identified by the MHRA and those highlighted internationally.

  - You are obliged to notify the MHRA of emerging safety issues within 3 working days after establishing that a signal or a safety issue from any source meets the definition of an emerging safety issue.

- **Risk Management Plans (RMPs)**

  - The MHRA will continue to accept EU versions of the RMP, but where they have made a specific request for information to be included this may need to be provided in a specific annex.

  - For CAPs the current approved version of the RMP should be included in the initiating sequence as part of the conversion process

  - RMPs and updates to RMPs for products authorised to be sold or supplied in the UK should be submitted to the MHRA via the appropriate variation procedure.

- **Periodic Safety Update Reports (PSURs)**

  - PSURS submitted after 1 January 2021

- The MHRA will continue to accept EU versions of the PSUR, but where the MHRA has made a specific request for information or where there is UK-specific information relevant to the benefit/ risk assessment this should be included in a specific annex.

- For now, the EU reference date (EURD) list should be followed and PSURs with submission dates after 1 January 2021 should be submitted to the UK at the same time as the EU.

- For products which are the subject of a UK MA, all PSURs with the same active/combination should be submitted as part of the same procedure.

  - The content and format will remain the same as currently required in the EU and the expectation is that the same PSUR will be submitted to the MHRA as to the EU.

  - Generally, you will not be required to re-submit PSURs which are submitted to the EU PSUR repository before 1 January 2021

- Unless the MA specified differently, PSURs for actives/combinations not currently on the EURD list (and so not subject to single assessment process) should be submitted to the MHRA at least every 6 months for the first 2 years after placing on the market and annually for the following 2 years and then every 3 years after that

- Outcomes of MHRA assessments will be issued shortly after publication of the EU assessment to maintain harmonisation with the submission requirements on the EURD list

- The MHRA have developed a submission portal for PSURs which will be ready for use from 1 January 2021 - PSURs can be submitted in PDF or Word or as part of a zip file (more detailed requirements for submission to be issued soon).

  - PSUR submissions are not required as part of the CTD lifestyle in the UK and should not be submitted as part of the initiating sequence in the conversion process for centrally authorised to GB MAs.

- A fee of £890 will be payable for the assessment of PSURs for actives/ combinations currently listed on the EURD (or future UK reference date list) which are submitted to the MHRA. This will be reduced to £445 for each PSUR where more than 1 PSUR is involved in the procedure. Following assessment, the outcome of PSUR assessment procedures will be published, including any amendments to the SPC and PL wording. No further fee will be payable for the amendment of the product information as a result of the UK

assessment which will generally be made by a Type IA variation.

- For GB only MAs, the PSUR should be submitted to the MHRA system.
- For products authorised to be sold or supplied in Northern Ireland, PSURs should be submitted in line with EU requirements and submitted to the EMA via the EU PSUR repository. The outcomes from the EU procedure should be implemented.
- PSURs for UK MAs covering both GB and Northern Ireland will need to be submitted to both the MHRA and EMA.

  - PSURs submitted before 1 January 2021

    - For GB only MAs where a PSUR has been submitted before 1 January 2021 but the EU single-assessment procedure has not been concluded, MHRA will assess the PSUR considering any relevant information, including any EU decision and any other further information they request, in order to make the assessment.
    - Where the PSUR is for a product authorised by a UK MA for both GB and Northern Ireland, the procedure will continue in line with the single-assessment procedure.
    - Where the assessment has been concluded but the outcome not implemented before 1 January 2021, the MHRA will take the necessary steps to implement the outcome.
      - Where this involves a variation to the MA, the application should be submitted taking into account the guidance on converting CAPs to Great Britain MAs where this applies.

- **Post Authorisation Safety Studies (PASS)**

  - Pass protocols and results submitted after 1 January 2021

    - For PASS where the study is a condition of the UK MA, the draft protocol should be submitted to the MHRA prior to the start of the study. It will be assessed in line with usual protocols.
    - Where the MA extends to Northern Ireland or is a Northern Ireland only MA, the draft study protocol should also be submitted to the Pharmacovigilance Risk Assessment Committee (unless the study is only to be conducted in the UK at the request of the MHRA).
    - For all PASSs that are non-interventional which are either voluntary or a condition of the MA and that involve collection of safety data from patients/healthcare professionals, the

final study reports should be sent to the MHRA for assessment.

- The final study report and an abstract of the study results should be submitted to the MHRA. Where the MA extends to Northern Ireland or is a Northern Ireland only MA, the study report should also be submitted to the Pharmacovigilance Risk Assessment Committee (unless the study was only conducted in the UK at the request of the MHRA).
  - The final study report should be submitted within 12 months of the end of data collection
  - The fee for assessment of PASS protocols or final study reports is £839.
  - Both protocols and final study reports should be submitted to us using the Type II complex variation route (classification C.I.13) with the corresponding fee.

- Ongoing issues regarding PASS protocols after 1 January 2021
  - For products authorised in the UK where the EU PRAC (Pharmacovigilance Risk Assessment Committee) has either endorsed a draft study protocol or made a substantial amendment to a draft protocol before 1 January 2021, the MHRA will accept the draft or amended draft study protocol but may request further information to be submitted within a specific time.
  - Where a non-interventional PASS has been proposed or imposed but the draft protocol has not been endorsed before 1 January 2021, any information required by the PRAC together with any information required by the MHRA regarding the protocol must be submitted directly to the MHRA, even if the information was submitted via the EU procedure prior to 1 January 2021.

- Ongoing issues with PASS final study reports after 1 January 2021
  - For products authorised in the UK, where a final study report was submitted to the EMA before 1 January 2021 but no recommendation was made before that date, it may be required that the study report and abstract of the study report are submitted to the MHRA together with any further information relating to the study
    - In any event, it's advisable to evaluate the impact of the results on the authorisation and submit a variation application as necessary.
  - Where PRAC made a recommendation prior to 1 January 2021, the MHRA will implement the agreed measures in line with the agreed timetable. You should submit any variation to

the MHRA (for converted CAPs please refer to the guidance on the website) and they will determine the application within the usual timeframes.

- **Safety Referrals**
    - For procedures started but not concluded before 1 January 2021 (e.g., where a CHMP/CMDh opinion had not been reached), the MHRA will complete the assessment and make a decision based on the information they have, including any decision made at EU level before 1 January 2021.
        - They may request further information regarding the procedure where appropriate.
    - Where the referral has been concluded but the decision not implemented before 1 January 2021, the MHRA we will take the necessary steps to implement the final decision.
- **Major Safety Reviews**
    - From 1 January 2021, where there are concerns regarding a medicine or class of medicines that are authorised in the UK, the MHRA may conduct a major safety review to review the available data and consider what regulatory action may be needed.
        - In these circumstances they will publicly announce the initiation of the review. This will outline the reasons for the review, the list of affected active substances and products, and the timescales for the review.
    - Where you hold an MA for an affected product, you will be notified of the start of and the reasons for the review, and will be provided with a list of questions that should be addressed by all MAHs along with the deadline for submitting the information.
        - In the first instance, this correspondence will be done via the Qualified Person for Pharmacovigilance (QPPV) but a different or additional contact for future correspondence can be nominated.
        - The outcome of the review will be published.
        - Where the recommendations include proposals for regulatory action the details of the measures to be taken including any changes to the product information will be published.
    - A major safety review will cost the following:
        - £51,286 where one or two active ingredients or combinations of active ingredients are included
        - £59,595, where three active ingredients, or combinations of active ingredients, are included

        - £67,904, where four active ingredients, or combinations of active ingredients, are included
        - £76,213, where five or more active ingredients, or combinations of active ingredients, are included
        - Where the review relates to 2 or more authorisations, the fee will be divided by the number of authorisations forming part of the review and you will pay that reduced fee for each relevant authorisation it holds.

- **Post-authorisation Measures (PAMs)**
    - Post-authorisation obligations in place on 1 January 2021 will remain in place (including specific obligations, Annex II conditions, additional pharmacovigilance activities in the RMP (MEA), legally binding measures (LEG) or recommendations).
    - For converted EU MAs the MHRA recommend using the current application forms for PAMs and submitting the information as a post-authorisation commitment, following the same principles for submission as for variations in the CAPs conversion guidance.
    - Where data relating to a PAM has been submitted before 1 January 2021 but the assessment has not been concluded the MHRA will conclude the assessment where appropriate.
        - For converted EU MAs, a copy of the application should be included in the data submission package.
    - Where your evaluation of data supporting a MEA or LEG suggests that an update to the product information is required, this should be submitted via a Type II variation application.

- **Implementation of outcomes of referrals and procedures concerning PSURs, PASS, signal assessments and PAMs**
    - Where an amendment to the product information is required as a result of the above procedures, this will be implemented via a variation procedure.
    - Where the procedure has been concluded before 1 January 2021 but the variation has not been submitted, the outcome will be implemented by the same procedure as for the EU (Type IA, Type IB or Type II).
    - Where there has been no EU decision before 1 January 2021, the MHRA will carry out their own assessment where appropriate and the outcomes of assessments will be published together with advice on implementation.

2. **Guidance on qualified person responsible for pharmacovigilance (QPPV) including pharmacovigilance system master files (PSMF) from 1 January 2021**

- From 1 January 2021, the following legal obligations will apply to holders of UK marketing authorisations:
    - To operate a pharmacovigilance system for UK authorised products.
    - To have 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.
    - To maintain and make available upon request a pharmacovigilance system master file (PSMF) that describes the pharmacovigilance system for UK authorised products. The PSMF must be accessible electronically or physically from the UK at the same site at which reports of suspected adverse reaction may be accessed.

PAEDIATRICS (3 guidance documents):

1. **Procedures for UK Paediatric Investigation Plan (PIPs) from 1 January 2021**

- General approach to UK Paediatric Investigation Plans
    - The MHRA will simplify the PIP application process for applicants by offering an expedited assessment where possible, and mirroring the submission format and terminology of the EU-PIP system.
        - Scientific content and assessment required will be kept in line with European Medicines Agency (EMA) guidance documents
    - Northern Ireland will continue to be a part of the EU's system for paediatric medicines development, including agreement of EU paediatric investigation plans (PIPs) or waivers.
    - The MHRA will take decisions on PIP and waiver opinions, modifications and compliance statements to support paediatric market authorisation decisions, while acknowledging that EU PIPs remain applicable for Northern Ireland.
    - The 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.

- A case by case discussion should always be considered for any UK paediatric submissions that do not fall into any of the prespecified criteria listed below.

- 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.

- For general enquiries about paediatric submissions including PIP and waiver applications, modification procedures, and compliance checks, contact the MHRA Paediatric Unit at ukpip@mhra.gov.uk.

- PIP Submissions

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

    - EU-PIPs and modifications agreed by the EMA prior to 1 January 2021, will be adopted as UK-PIPs on or after that date and these PIPs will not require re-submission to the MHRA.

    - Where a valid request for an EU-PIP or modification or waiver has been made to the EMA, but no decision has been given before 1 January 2021, the EU-PIP will be adopted as a UK-PIP if the EMA Paediatric Committee (PDCO) has given a positive opinion with which the UK has concurred. These PIPs will not require re-submission to the MHRA.

    - Where a valid request for an EU-PIP or modification or waiver has been made to the EMA, but the PDCO has issued a negative opinion, the MHRA will treat the application as refused but the applicant can submit an updated PIP to the MHRA which addresses the reasons for refusal.

    - Where a valid request for an EU-PIP or modification or waiver has been made to the EMA, but the PDCO has not yet given any opinion, or where the UK disagreed with the PDCO opinion, these PIPs should be resubmitted to the MHRA unless the applicant notifies 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 1 January 2021 that have been assessed and agreed by the MHRA, will be referred to as agreed UK-PIPs.

  - UK-PIP submissions after 1 January 2021

    - In order to establish the MHRA assessment process, when a UK-PIP is submitted, 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.

- UK-PIP with agreed EMA opinion from 1 January 2021 or ongoing assessment at EMA from 1 January 2021
  - In principle, the MHRA will aim to accept a positive PDCO opinion. 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 (such as a new drug class, mechanism of action);
    - 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).
  - A full assessment may be requested by the applicant.
  - If the PDCO opinion is negative, the 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 despite PDCO negative opinion, the applicant should consider incorporating changes to the UK-PIP during clock-stop, for the elements that received a negative PDCO assessment.

        - If a UK-PIP has been withdrawn and a new UK-PIP submitted, the new PIP will undergo review using the same assessment criteria as mentioned above.

    - UK-PIP with no EU-PIP from 1 January 2021

        - Full assessment of the UK-PIP is required. The applicant should also 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;

            - 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

    - Modification of an adopted or agreed UK-PIP

        - For both adopted and agreed UK-PIPs, when a PIP modification is submitted, it should be confirmed 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

            - 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 should include the most recent PDCO opinion and PIP SR.

        - For Agreed UK-PIPs, there will be either a focused assessment in cases where the EU opinion for the initial UK-PIP was accepted by the MHRA, or a full modification assessment in cases where the initial UK-PIP underwent full assessment.

        - The applicant may request a full assessment.

- UK-PIP modification of an agreed EMA opinion or ongoing assessment at EMA
    - In principle, the MHRA will aim to accept a positive PDCO opinion on modifications in cases where the initial UK-PIP was agreed on the basis of an agreed EU-PIP. A focused assessment may be needed if the criteria in (c) above are met.
    - If the PDCO opinion is negative whilst the UK assessment is ongoing:
        - The applicant has the option to withdraw the UK-PIP modification request or continue with the MHRA assessment.
        - Once a PIP has been withdrawn, a new UK-PIP modification can be submitted and will undergo review using the same assessment criteria discussed in (c) above.
        - If continuing 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
    - If there is no agreed EMA modification opinion a full assessment of modification will be required.
    - If the PDCO opinion is negative whilst the UK opinion is ongoing:
        - The applicant has the option to withdraw the UK-PIP modification request or continue with the MHRA assessment.
        - Once a PIP has been withdrawn, a new UK-PIP modification can be submitted and will undergo review using the same assessment criteria discussed in (c) above.
        - If continuing 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
    - If there is no agreed EMA modification opinion a full assessment of modification will be required.

- Class Waivers

- Submission of Paediatric Class Waiver
  - The current EMA class waivers list will be adopted by the UK from 1 January 2021.
  - In principle, the MHRA will aim to accept a positive EMA opinion on a class waiver request. Where there is no EMA opinion, a MHRA assessment will be undertaken.
  - For a negative EMA opinion on whether a Class Waiver applies:
    - The applicant should submit a full product specific waiver request for MHRA assessment which should include 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
  - Adopted UK-PIP Compliance check (CC)
    - A positive PDCO CC or interim CC will be adopted as the UK CC outcome unless subsequent modifications have led to divergence between the UK- and EU-PIPs.
    - However, the applicant must pay 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.
    - The PDCO compliance outcome documents should be submitted ahead or at the time of MA application. The format and submission procedure for UK-PIP applications will be published separately.
  - Agreed UK-PIP CC
    - A UK assessment is required for full or interim CC if:
      - there is any scientific divergence between the agreed UK-PIP and the EU-PIP
      - there is no PDCO CC.
    - The MHRA will adopt the PDCO CC outcome if:
      - there is a positive PDCO CC
      - the UK-PIP is equivalent to the EU-PIP

        - 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 similar to those noted in 4(a) above.

    - Non-compliance

        - For non-compliance 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 streamlined assessment 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 non-compliant 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

        - An MHRA statement of compliance when all of the agreed PIP measures have been completed, will be issued as follows, if appropriate, when an MA application (initial, extension or variation) is granted:

            - "The development of this product has complied with all measures in the agreed paediatric investigation plan < reference number >".

        - 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)

    - Regarding the applicant's paediatric study plans (PSP) agreed by the US Food and Drug Administration (FDA), applicants should provide the agreed PSP as part of their UK-PIP submission.

- Unmet needs in the UK paediatric population

    - The unmet needs for the UK paediatric population will be 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;

- products which are intended to be authorised as orphan medicines.

- This guidance will apply from 1 January 2021 in line with the Human Medicines Regulations (Amendment etc.) (EU Exit) Regulations 2019.

- 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.

2. Completed Paediatric Studies - submission, processing and assessment from 1 January 2021

- Legal background and scope

  - Regulation 78A(13) and (14) of the Human Medicines Regulations 2012, as inserted by the Human Medicines (Amendment etc.) (EU Exit) Regulations 2019, requires that holders of a UK marketing authorisation 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 regardless of whether the studies are conducted in accordance with an agreed PIP or where the MAH intends to apply for a marketing authorisation for a paediatric indication in relation to the product

  - These provisions replace Article 46 of Regulation (EC) No 1901/2006 (the 'Paediatric Regulation').

  - MHRA will also consider the outcome of CMDh paediatric work-sharing procedures (PdWS) reviewed under Article 45 of Regulation (EC) No 1901/2006 (as amended). If required, MHRA will request updates to the product information (PI) for UK Marketing Authorisations.

- Submission of information

  - The MAH must submit a cover letter [Suggested cover letter template here] within 6 months of completion (i.e., date of last visit of last subject undergoing the trial, unless otherwise justified

in the protocol) of the concerned paediatric studies to the MHRA in eCTD format to this mailbox: paediatricstudies@mhra.gov.uk.

- 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. If this is the case, 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. If this is the case, the MAH should:
    - specify the UK procedure number, if available or the type of application this will be submitted under
    - confirm that the application will be submitted within the next 6 months
    - 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
  - On receipt of the cover letter, MHRA will carry out an initial appraisal of whether an assessment procedure is required. One of the following may apply:
    - No data assessment is required at this stage and MHRA will maintain records including justification for the decision, e.g., that a regulatory submission to vary the Marketing Authorisation is planned in the next 6 months, or any other agreed reason(s) to defer the procedure.
    - Limited evaluation of the study data may be undertaken if the MAH provides robust justification that the study data are unlikely to warrant product information (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 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 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 on 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 UK (for example hay fever to specific seasonal pollen found in non-UK countries);
- other justification as to why a detailed assessment is not required at this stage.

If one of the above criteria are met, 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 MHRA agrees with the MAH's justification not to update the PI.

- If review of the data is required (when the MAH proposes a PI update or when MHRA concludes after the initial appraisal, that a full assessment is needed to robustly conclude on prospective PI updates), 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, including information on the pharmaceutical formulation used in the study, the existence of a suitable paediatric formulation and if relevant, conditions for an extemporaneous formulation.
  - 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.

- 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, they must justify the delay and propose a new submission date.

- Transitional provisions

  - If the results of a paediatric study have been submitted to EMA or CMDh under Article 46 of Regulation (EC) 1901/2006 prior to 1 January 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 product information (PI) is required.

  - Upon finalisation of the EU procedure and availability of the final assessment report, MAHs should submit this to paediatricstudies@mhra.gov.uk.

  - 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, 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

Steps	Day	Action
1	0	Receipt of letter notifying MHRA of completed study from MAH (see suggested template) via paediatricstudies@mhra.gov.uk
2	7	Allocate procedure to medical assessor
3	14	Inform MAH whether assessment of the data is required: A). If required, a variation is requested within 60 days, details of a submission package is described in section 2.3 of Submission of information, go to step 4, B). If an EMA P46 or CMDh PdWS under Article 46 of Reg.1901/2006 has been

		completed prior to 1 January 2021 and PI changes is a direct implementation to relevant UK products, step 11, C). If not required, MAH will be informed that no further action is needed
4	14	MAH submits data as variation type II, followed by Validation process (up to 14 calendar days)
5	Clock starts: 0	Provide MAH with start date of procedure
6	Standard: 59/60 (in exceptional circumstances for Extended: 89/90)	Preliminary AR followed by clock-stop period if there is a need for RFI or Preliminary/Final AR, where changes to the PI could be implemented at the end of the procedure if applicable
7	Clock-stop	Clock-stop period 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)
8	Standard: 60 (Extended: 90)	Final AR sent to MAH, where changes to the PI could be implemented at the end of procedure if applicable
9	Standard: 75 (Extended: 105)	Draft Public paediatric AR sent to MAH to comment on any confidential/commercial sensitive information within 15 days
10	Standard: 90 (Extended: 120)	Publish Public paediatric AR on MHRA website
11	60	If step <3b> is applicable, 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 work sharing procedures

    - MAHs are not required to submit to the MHRA information on paediatric studies completed by 26 January 2007 and which fall

under the remit of Article 45 of Regulation (EC) No 1901/2006 work sharing procedure.

- MHRA will monitor the published Public Assessment Reports (PAR) of Article 45 PdWS procedures. Once 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 MHRA considers that the MAHs should provide supplementary data in order to conclude on potential PI changes for the UK products and further UK assessment is deemed necessary, a type II variation could be requested within 60 days.
- Please direct any queries to specialpopulationsunit@mhra.gov.uk.

3. Format and content of applications for agreement or modification of a Paediatric Investigation Plan and requests for waivers or deferrals and concerning the operation of the compliance check from 1 January 2021

- See attached Guideline on the format and content of applications for agreement or modification of a Paediatric Investigation Plan and requests for waivers or deferrals and concerning the operation of the compliance check
- This document follows the format of the European Commission's best practice guidance.
- This guidance provides detailed information on
  - the required format and content of applications for agreement on or modification of a PIP
  - requests for waiver and deferrals
  - the operation of the compliance check in accordance with the HMRs.

- The legal requirements for UK-PIPs are set out in the Human Medicines Regulations 2012, as amended by the Human Medicines (Amendment etc.) (EU Exit) Regulations 2019 (HMRs), including transitional provisions (see in particular regulations 50A to 50D).

- This document should be read in conjunction with Guidance on procedures for UK-PIPs from 1 January 2021 and User reference guides on using the MHRA Submissions homepage for PIP-related submissions (available from the MHRA Submissions homepage).

- PIPs, waivers, annual reports, and compliance checks should be submitted via the MHRA Submissions homepage

- Submission of a PIP must be made to the MHRA no later than the completion of the human pharmaco-kinetic studies in adults in relation to the medicinal product to which the plan relates, unless the MHRA agrees to accept a later request. This is according to regulation 50B of the HMRs. It is our intention to update these Regulations to reflect the change of implementation dates following the Transition Period.

- Applications for marketing authorisations to MHRA to which the PIP provisions apply should contain either:

    - the results of all studies of an agreed PIP with details of all information collected in compliance with this PIP;

    - a decision granting a deferral on an agreed PIP (subject to compliance check);

    - a decision granting a product specific waiver;

    - the European Medicines Agency (EMA) decision number granting a class waiver, and if the applicant has requested it, the confirmatory letter from the EMA and/or MHRA confirming the medicinal product for the intended condition falls under the class waiver.

- For guidance on the submission, see processing and assessment of all completed paediatric studies sponsored by Marketing Authorisation Holders (MAHs).

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