The withdrawal of the UK from the European Union was fully effective on 1 January 2021, with the Medicines and Healthcare products Regulatory Agency (MHRA) becoming the UK’s standalone medicines and medical devices regulator. Medicine developers need to be aware of the rules they now have to follow for getting their products approved for the UK market. MHRA has published extensive guidance, and this article aims to highlight the most relevant initiatives.

Introduction
On 29 March 2017, the UK notified the EU of its intention to withdraw from the EU,¹ an event that became known as Brexit. The UK formally left the EU on 31 January 2020. A transition period began on 1 February 2020 and was due to end on 31 December 2020. During this period, the UK withdrew from participating in EU institutions, including the European Medicines Agency (EMA), but the EU pharmaceutical law remained in effect in the UK. Since 1 January 2021, EU pharmaceutical law is no longer in effect in the UK, except for Northern Ireland, based on the Protocol on Ireland/Northern Ireland. The Protocol is part of the
withdrawal agreement between the EU and UK that established the terms of the UK’s withdrawal from the EU (Figure 1).

Since May 2017, the EMA, the European Commission (EC), and the national competent authorities in the EU member states have been working together to minimize the impact of Brexit on the supply of medicines, advising companies on how to apply for and implement the necessary changes and encouraging them to plan and act early. In parallel, the EMA and the EU member states reassigned the UK’s portfolio of more than 370 centrally authorized medicines to rapporteurs and co-rapporteurs from two of the remaining EU member states, Iceland and Norway (Figure 1). A rapporteur is a member of the European Parliament selected to assess a legislative proposal and, based on discussions with members of the overseeing committee, compiles report or opinion on the proposal for the committee.²

Soon after the UK’s 2017 announcement of its withdrawal from the EU, the MHRA began preparations to ensure it would be fully independent by the January 2021 deadline. The MHRA is now the sole decision-maker regarding authorization of medicines and medical devices in the UK, except for decisions on marketing authorization applications (MAAs) made through the European procedures to market products in Northern Ireland.³ This means that the marketing authorizations (MAs) issued by the MHRA for novel products will be valid only for Great Britain (England, Wales, and Scotland).

The MHRA is a globally recognized regulatory agency and intends to remain so in the post-Brexit era. One of the agency’s priorities is to continue supporting and enhancing innovation and to accelerate routes to market.⁴ It aims to achieve those goals in a timely and pragmatic manner by echoing some existing EU regulatory practices, such as the accelerated assessment (AA) and conditional marketing authorization (CMA), and has launched some abbreviated procedures by relying on decisions granted at the EU level.

**Figure 1. Brexit timeline**

29 March 2017
UK announces intent to exit from EU

1 January 2017

1 January 2018

1 January 2019

1 January 2020

1 January 2021

1 January 2021 - 30 April 2021
UK Pharmaceutical Law in effect except for Northern Ireland; MHRA Standalone Regulator

1 February 2020 - 31 December 2020
Transition period: exit from EMA, pharmaceutical law remains in effect

1 May 2017 - 31 January 2020
Preparation for Brexit, redistribution of MHRA portfolio

31 January 2020
UK exits from EU

30 April 2021

EMA, European Medicines Agency; MHRA, Medicines and Healthcare products Regulatory Agency
But the MHRA has also developed innovative and expedited licensing routes, such as the innovative licensing and access pathway (ILAP) and the rolling review (RR), and has joined Project Orbis and Access Consortium, two initiatives for building synergies and sharing knowledge among international regulators to enhance the efficiency of regulatory submissions and assessment systems for key products, such as cancer therapies.

Grandfathering of centrally authorized products

All existing centrally authorized product (CAP) MAs were automatically converted into Great Britain (GB) MAs on 1 January 2021, except when the marketing authorization holders (MAHs) opted out of conversion, in which case their product(s) will no longer be licensed and marketed in Great Britain. These GB MAs, referred to as “converted EU MAs,” were assigned one or more GB product license numbers based on existing UK practice. MAs for CAPs not currently marketed in the EU or UK can still be converted to GB MAs (Figure 2). For the purposes of operating, the sunset clause will be restarted from the date of conversion to a GB MA. Existing CAPs remain valid in Northern Ireland. Under the sunset clause, a medicine’s MA will no longer be valid if the medicine does not reach the market within 3 years of it being authorized.

Figure 2. Conversion of centrally authorized product to GB product license

- eCTD, electronic common technical document; PLBG, GB product license.
Holders of converted EU MAs have a year, beginning 1 January 2021, within which to submit baseline product data in the form of an initiating electronic common technical document (eCTD) sequence for each converted EU MA. This initiating sequence must include all current, approved information of the converted EU MA on the data submission date to the MHRA, except periodic safety update report information and historic EU information about the pharmacovigilance system master file, which can be removed. This makes sense because the initiating sequence will be used as the start of the lifecycle for the nationally registered product and must therefore include information relevant only to Great Britain (Figure 2).

In some circumstances, the initiating sequence can be submitted in two steps within the 1-year period, in the form of a minimal initiating sequence followed by a complete initiating sequence. Variations to the converted EU MAs will be considered by the MHRA only after the baseline information has been submitted and processed. For the purpose of renewals, a converted EU MA will have the same renewal date in the UK as in the EU.

New ‘reliance’ procedures

The MHRA has launched two “reliance” routes allowing the MHRA to offer an abbreviated assessment procedure of 67 days for products that have already gone through the EU centralized, decentralized, and mutual recognition procedures.

The EC Decision Reliance Procedure (ECDRP) allows applicants to seek a GB MA that relies on the decision taken by the EC in respect of a new MA for the same product under the centralized procedure (CP). The applicant should submit a letter of intent to submit an ECDRP to the MHRA if a positive opinion from the EMA Committee for Medicinal Products for Human Use (CHMP) is anticipated and at least 4 weeks before submission of the ECDRP MAA. Then, the ECDRP MAA has to be submitted to the MHRA as a single eCTD sequence on receipt of the positive CHMP opinion on Day 210 of the CP, or as soon as possible after this date (Figure 3, p. 5). When the ECDRP is submitted within 5 days of the CHMP positive opinion, the date of the opinion will be designated Day 0 of the ECDRP, and the GB MA will be granted as soon as possible following submission of confirmation of the EC decision. The applicant is responsible for providing the EC decision to the MHRA on the day that it is received. If the ECDRP MA is submitted more than 5 days after the CHMP positive opinion, Day 0 of the ECDRP will be the date of MAA validation and the GB MA may be delayed.

Applicants who had CAP applications pending approval on 1 January 2021 but which had reached Day 120 or Day 181 of assessment in the CP, can also opt for the reliance route. The applicant will need to wait for the CHMP positive opinion and then apply for a GB MA. Alternatively, the applicant may submit the same application to the MHRA as has been submitted to the EMA. The MHRA will take into account any evaluation that has already been conducted by the EMA before
Figure 3. The European Commission Decision Reliance Procedure

1 January 2021, with a view to completing its own assessment of the application while the CP is ongoing, but no later than the issue of the EC decision. This second approach is known as “in-flight assessment.”

The ECDRP is expected to be operative until the end of 2022.

The Decentralised and Mutual Recognition Reliance Procedure can be used to apply for a UK or GB MA. In this case, the MAA will rely on the MA decision granted at EU level. Applicable to both reliance procedures, if major objections are identified or substantial amendments to the product information are necessary, the timetable will move to the standard national procedure timetable.

Innovative Licensing and Access Pathway

The ILAP is a new pathway aimed at reducing the time to market for innovative medicines. It allows applicants access to enhanced regulatory and other stakeholders’ input through collaboration between the MHRA, health technology assessment bodies, such as the National Institute for Health and Care Excellence (NICE) and the Scottish Medicines Consortium (SMC), the National Health Service England and NHS Improvement (NHSE&I), the Health Research Authority and the National Institute for Health Research. Applicants are encouraged to include the view of patient organizations.

The first step in the ILAP is the innovation passport application, which is the entry point to the ILAP (Table, p. 5). The innovation passport (innovative medicine designation) is open to commercial and noncommercial developers of
Eligibility criteria for innovation passport

<table>
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<th>Life-threatening/seriously debilitating condition OR significant patient or public health need.</th>
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<td>The medicinal products fulfils one or more of the following areas:</td>
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<td>• Innovative medicine, such as an ATMP, or new chemical or biological entity, or novel drug device combination;</td>
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<tr>
<td>• The medicine is being developed in a clinically significant new indication;</td>
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<tr>
<td>• Medicine for rare disease and/or other special populations (neonates, children, elderly, pregnant women); and/or</td>
</tr>
<tr>
<td>• Development aligns with the objectives for UK public health priorities.</td>
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Potential to offer benefits to patients (improved efficacy or safety, contribution to patient care or quality of life),

• Can be based on nondiagnostic data in valid models if clinical data is not yet available at an early stage;
• Applicants are encouraged to include in their evidence the views from patients or patient organizations around the benefit of a product, if available.

medicines at the preclinical through to mid-development stage. However, applicants are encouraged to apply early in the development of their products if they are to gain maximum benefit.

After submitting the application for an innovation passport, the applicant will be invited (usually within 4 to 6 weeks) to meet with the MHRA to discuss how the product fulfils the criteria. The evidence required for a product to fulfil the criteria will depend on where the product is in the development pathway. The MHRA and its permanent partners in this program, the NICE and the SMC, will jointly decide if the criteria have been fulfilled and will communicate the outcome of the assessment to the applicant within another 4 weeks.

The innovation passport designation opens the access to the target development profile (TDP), a product-specific development roadmap. The TDP is a living document that will be updated along the development program as new data are generated. The TDP is supported by a set of tools known as the TDP toolkit, which can be selected to design an efficient development program. Available tools include continuous benefit-risk assessment that integrates real-world evidence, adaptative inspections, novel methodology and innovative clinical trial design, patient recruitment assisted with the Clinical Practice Research Datalink, innovative and flexible licensing routes (AA, RR, CMA, AEC, Project Orbis, Access Consortium), and other tools.

The innovation passport holder should complete and submit a TDP form gathering relevant information about the product development, evidence generation plan, scientific advice, patient engagement, and so on. After the form has been submitted, the innovation passport holder will meet the MHRA and partners and indicate which tools from the TDP toolkit they are interested in using. The MHRA and partners will the develop the TDP roadmap, which will be provided to the medicine developer within 4 to 6 weeks.
The innovation passport does not replace the existing promising innovative medicine designation of the early access to medicines scheme, and applicants can apply to both.

**Rolling review**
The RR is a new route in the UK for MAAs intended to enhance development of novel medicines by offering ongoing regulatory interaction and advice. The process is envisaged as a phased, modular, approach with the applicant submitting modules of the eCTD dossier incrementally for pre-assessment, permitting early identification of issues. Each assessment cycle lasts 60 days, with a module assessment summary issued at the end of the cycle. The final phase entails the submission of the consolidated full dossier.

**Orphan drug designation**
There is no premarketing authorization orphan designation in the UK as there is in the EU. Applications for orphan designation will be assessed by the MHRA at the time of the MA, and a decision on orphan status will be made at the time of the decision on approval of the MA.

Criteria for designation remains the same than in the EU, but relative only to the population of Great Britain, so that prevalence in Great Britain is not more than 5 persons in 10,000 of the population and there are no satisfactory therapies for the condition in Great Britain (or if such therapy exists, the medicine is of significant benefit to those affected by the condition).

Products with an EU orphan designation can be considered for a GB orphan MA. A UK-wide orphan MA can only be considered in the absence of an active EU orphan designation. If a UK-wide orphan MA is granted and the medicinal product subsequently receives EU orphan designation, the MAH would need to submit a variation to change this to a GB orphan MA.

Authorized orphan medicines are granted with up to 10 years of market exclusivity, with additional 2 years when results of studies from a pediatric investigation plan (PIP) are included in the product information. The market exclusivity period starts the date of first approval of the product in Great Britain. The market exclusivity period will be reduced to 6 years if the orphan criteria are no longer met in relation to the medicinal product.

Remaining market exclusivity periods for orphan CAPs granted before 1 January 2021 that have been converted to GB MAs will continue to apply, and it is not necessary to submit orphan maintenance reports to the MHRA, although they can be provided as additional information.

**Pediatric investigation plan**
Parallel submission of PIPs to EMA and MHRA is strongly supported by both agencies to allow robust parallel assessment and finally, alignment of the agreed pediatric plans across jurisdictions.
The MHRA facilitates the preparation of UK-PIPs by mirroring the submission format, content, and terminology of the EU-PIP. However, applicants should include information relevant specifically to the UK, in particular with respect to areas of unmet therapeutic need.

As with the EU-PIP, the UK-PIP application should be submitted soon after upon completion of the human pharmacokinetic studies, unless the MHRA agrees to accept a later submission.

The MHRA offers an expedited assessment of PIPs where possible. It is therefore important the applicant informs the MHRA on whether there is an agreed EU-PIP or an ongoing EU-PIP and its timeline in the pediatric committee (PDCO) assessment; also, about any scientific divergence between the submitted UK-PIP and the EU-PIP. If a PSP has been agreed by the US FDA, it should be provided as part of the UK-PIP submission.

EU-PIPs with an EMA decision agreed before 1 January 2021 do not require re-submission to the MHRA and will be adopted as UK-PIPs. EU-PIPs submitted, but without an EMA decision before 1 January 2021, will be adopted as UK-PIPs if the PDCO has given a positive opinion before 1 January 2021 and do not require resubmission to the MHRA. EU-PIPs with a PDCO negative opinion will be treated by the MHRA as refused, but applicants can submit an updated PIP to the MHRA which addresses the reasons for refusal.

The MHRA will aim to accept a positive PDCO opinion on PIP modifications in cases where the initial UK-PIP was agreed on the basis of an agreed EU-PIP.

Current EMA class waivers list is adopted by the UK from 1 January 2021. In principle, the MHRA will aim to accept a positive PDCO opinion on a class waiver request. An EU full product specific waiver with a positive PDCO opinion or EMA decision before 1 January 2021 will be adopted as a UK full waiver, with no submission to the MHRA required.

**Medical devices**

Since 1 January 2021, all medical devices, including the in vitro diagnostic medical devices (IVDs), placed on the GB market need to be registered with the MHRA, although there is grace period which varies depending on the device class.

The CE marking and certificates issued by EU-recognized notified bodies will continue to be recognized in Great Britain until 30 June 2023. From 1 July 2023, new devices placed on the GB market will need to comply with UK conformity assessed, or UKCA, marking requirements.

Manufacturers not based in the UK wishing to place a device on the GB market need to appoint an UK Responsible Person who will take responsibility for the product in Great Britain.
The provisions contained within the EU Medical Device Regulation and EU In Vitro Diagnostic Regulation will not be transposed into law, and therefore not implemented, in Great Britain.

**IT systems**

The MHRA has developed its own submission portal, the MHRA Submissions, for regulatory submissions, clinical trial–related submissions, and vigilance activities for UK and GB licenses.

Once the registration for MHRA Submissions is completed, MHRA Submissions company administrators can register for the MHRA Gateway, the platform for submission of individual case study reports (ICSRs) and suspected unexpected serious adverse events reports (SUSARs). If the company does not have the capability to use the MHRA Gateway, it can register for the ICSR Submissions portal to send ICSRs and SUSARs to the MHRA.

**Miscellaneous**

The marketing authorization holder for a UK MA must be established in the UK, that is, Great Britain or Northern Ireland, or in the EU or EEA (Figure 4).

The qualified person responsible for pharmacovigilance (QPPV) for UK nationally authorized products (including those that cover Northern Ireland, Great Britain, or the whole of the UK) can reside and operate anywhere in the UK, the EU, or EEA. Where the QPPV does not reside and operate in the UK, there will be a

**Figure 4. Relationships between various multinational European organizations and agreements**

need for a national contact person for pharmacovigilance who resides and operates in the UK.  

The sponsors (or their legal representatives) of clinical trials taking place in the UK must be established in the UK or in a country included in the MHRA’s approved country list, which includes the EU and EEA countries.  

Conclusion

Regulatory decisions on medicinal products in the UK (with the exception of Northern Ireland) are no longer taken by the EMA, but by the MHRA as sole and independent regulatory body. Given its relevance, it is expected that the majority of drug developers will continue to include the British market in their strategic plans, which makes it necessary for them to be aware of the new game new rules in the UK regarding the authorization of medicines and medical devices.

Abbreviations

AA, accelerated assessment; ATMP, advanced therapy medicinal product; CAP, centrally authorized product; CHMP, Committee for Medicinal Products for Human Use; CMA, conditional marketing authorization; CP, centralized procedure; EC, European Commission; ECDRP, European Commission decision reliance procedure; eCTD, electronic common technical document; EEA, European Economic Area; EMA, European Medicines Agency; EU, European Union; FDA, Food and Drug Administration; GB, Great Britain; ICSR, individual case study report; ILAP, innovative licensing and access pathway; IVD, in vitro diagnostic medical device; MA, marketing authorization; MAA, marketing authorization application; MAH, marketing authorization holder; MHRA, Medicines and Healthcare products Regulatory Agency; NICE, National Institute for Health and Care Excellence; NHS, National Health Service; PDCO, pediatric committee; PIP, pediatric investigation plan; QPPV, qualified person responsible for pharmacovigilance; RR, rolling review; SMC, Scottish Medicines Consortium; SUSAR, suspected unexpected serious adverse events reports; TDP, target development profile; UK, United Kingdom; US, United States.

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