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A Guide to the UK Regulation of Medicines and Medical Devices Post-Brexit

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INTRODUCTION

UNITED KINGDOM

The impact of the 2016 EU Referendum on the regulation of medicines and medical devices cannot be underestimated. Throughout the transition period to the UK formally leaving the EU (January 2021), the Medicines and Healthcare products Regulatory Agency (MHRA) and the UK Government made efforts to minimise this impact. Now the MHRA is the standalone regulator for safe and effective medicines and medical devices in the UK.

This guide highlights the changes that have been made to UK regulation and shares the latest developments that have been established to streamline the process. One of the ambitions of leaving the EU was for the UK to become a science superpower and global leader of research and innovation. Whether this happens remains to be seen, but any pharmaceutical or medical device company should be aware of the changed regulatory landscape.

Our aim has been to keep this guide as simple as possible because this subject has left in its wake many detailed documents and legal discussions. This is intended as a summary of regulations as of the date of publication. It is not intended to provide legal or regulatory advice. We hope you find it useful.

HOW THE EU REFERENDUM RESULT CHANGED REGULATORY APPROVALS

The EU Referendum in 2016 led to the UK notifying the European Union (EU) of its intention to withdraw from it. Transition from the EU allowed the UK to offer fully independent regulatory decisions for both medical devices and pharmaceuticals, both nationally and jointly with other international regulators.

From 2017, the European Medicines Agency (EMA) and EU member states worked to minimise the impact of Brexit on the supply of medicines and reassigned the UK's portfolio of previously centrally authorised medicines.

The MHRA worked closely with the Government to decide the best options for the safe and effective regulation of medicines and medical devices in the UK. While negotiations with the EU continued, the UK remained a full and active member of the EU, with all the rights and obligations of EU membership.

From 2019, National submissions only were permitted within Great Britain. Registration for the MHRA portal was necessary for any subsequent submissions. The MHRA portal is not new. It wasn't created because of Brexit; rather it already existed to support National procedures in the UK. However, it's now the only route to yield MHRA approvals. The UK no longer has access to the European authorisation routes (either the centralised procedure (CP), mutually recognised procedure (MRP), or decentralised procedure (DCP) routes). Most member states have their own portals to support national procedures. However, EU member states have the option of involvement in centralised, or mutually recognised procedures, which in theory should be less onerous than multiple local (national) registrations which utilise additional submission pathways.

The UK formally left the EU on 31 January 2020, withdrawing from participating in EU institutions, including the European Medicines Agency (EMA). During the transition period, the UK government amended the Human Medicines Regulations 2012 (HMRs) by the Human Medicines (Amendment etc.) (EU Exit) Regulations 2019 and 2020 legislations. In effect, this allowed continued reliance on EU guidance as they stood immediately before the end of the transition period. Furthermore, this changed the legal basis of applications in the UK (Table 1).

During the transition phase, the UK Parliament drafted a EU–UK Trade and Cooperation Agreement, and the European Parliament ratified the agreement in late April 2021. The EU and UK agreed to apply the draft agreement with effect from 1 January 2021.

Any EU legislation since this date does not automatically apply in the UK. For example, since the new EU Clinical Trials Regulation took effect after the transition period had expired, it was not automatically incorporated into UK legislation.

Type	EU Directive 2001/83/EC	MHRA legal basis
Full application	Article 8(3)	Regulation 50/50A/50B*
Generic application	Article 10.1	Regulation 51/51A/51B*
Hybrid application	Article 10.3	Regulation 52/52A/52B*
Similar biological application	Article 10.4	Regulation 53
Well-established use application	Article 10a	Regulation 54
Fixed-combination application	Article 10b	Regulation 55
Informed consent application	Article 10c	Regulation 56

Table 1. Types of marketing authorisation applications to the MHRA. * No suffix: UKMA(NI). A: UKMA(GB). B: UKMA(UK). Herbal and homeopathic products not included. Source: https://www.gov.uk/guidance/types-of-application-legal-basis

EU MARKETING AUTHORISATIONS

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. All existing centrally authorised product (CAP) marketing authorisations (MAs) were automatically converted into Great Britain (GB) MAs on this date (referred to as converted EU MAs), except when the marketing authorisation holders (MAHs) opted out.

Where the MAHs opted out their product(s), these medicines and medical devices are no longer licensed and marketed in GB. 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 three years of authorisation or conversion to a GB MA.

MAHs who hold converted EU MAs had until 01 January 2022, to submit baseline product data in the form of an initiating electronic common technical document (eCTD) sequence for each converted EU MA.

APPROVALS IN NORTHERN IRELAND

As a result of the Northern Ireland protocol, different rules apply in Northern Ireland. Broadly speaking Northern Ireland will continue to follow the EU regulatory regime, but its national competent authority remains the MHRA. This means that the GB MAs issued by the MHRA, whilst not technically valid for Northern Ireland, will allow for distribution of GB product into Northern Ireland via the Northern Ireland MHRA Authorised Route (NIMAR).

While GB MAs (which technically only covers England, Scotland, and Wales) nominally exclude Northern Ireland, and EU centralised procedures (CPs) cover Northern Ireland, 'import' of a 'GB' drug into Northern Ireland is still permitted. This is a seemingly small detail but does run counter to the CP approval. This means that both an EU approved drug and GB approved drug can be available in Northern Ireland. This was covered by a rather subtle press release issued in April 2022 but wasn't wasn't widely broadcast. The proposal was planned to come into effect as European legislation as a matter of urgency and will cover Northern Ireland indefinitely.

NEXT STEPS FOR THE MHRA

The MHRA's intention is to remain a globally recognised regulatory agency in the post-Brexit era. According to the MHRA Corporate Plan 2018 to 2023, a priority is continuing to support innovation and to accelerate routes to market. The MHRA wishes to be seen as a "globally unique concentration of expertise in data, standards and regulation," and its plan over the next few years is ambitious.

Since the transition period, the MHRA has also launched some reliance procedures. The UK also has a 150-day assessment for 'high quality' national applications aimed at accelerating assessments. Rolling Review 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 uses a phased, modular, approach with the applicant submitting modules of the eCTD dossier incrementally for pre-assessment, permitting early identification of issues. This was extensively used for COVID-19 therapies and vaccines.

For example, the reliance procedures offers an abbreviated assessment procedure of 67 days for products that have already gone through the EU centralised, decentralised, and mutual recognition procedures. However, the ECDRP is likely to be replaced with a new international reliance framework from 2024 while the Guidance on the decentralised and mutual recognition reliance procedure (MRDCRP) will remain in place.

The MHRA has also developed innovative and expedited licensing routes, such as the innovative licensing and access pathway (ILAP) and the rolling review (RR). It has also joined Project Orbis (a programme to review and approve promising new oncology products initially reviewed by the FDA) and Access Consortium (a coalition of regulatory authorities together with Australia, Canada, Singapore and Switzerland), two initiatives in which international regulators share knowledge. The aim is to improve the efficiency of regulatory submissions and assessment systems for key products, such as cancer therapies.

Advanced therapy medicinal products (ATMPs) and biosimilar products will be regulated in GB by the MHRA according to the same principles that previously applied. However, the MHRA issued biosimilar guidance in early 2021 which places greater emphasis on quality and the confirmatory clinical PK study. Northern Ireland will continue to follow the EU regulatory framework.

THE INNOVATIVE LICENSING AND ACCESS PATHWAY

According to the MHRA this new pathway aims to accelerate the time to market and facilitate patient access to medicines. These medicines include new chemical entities, biological medicines, new indications, and repurposed medicines.

The ILAP 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 organisations. MAHs need to apply for an 'innovation passport' (called the innovative medicine designation), and this initiative applies to both commercial and non-commercial developers of medicines from preclinical through to mid-development stages if the programme fulfils the criteria (below).

Applicants are encouraged to apply early in product development to gain maximum benefit. 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.

The ILAP is technically a pathway for England, Scotland, and Wales, the countries constituting GB. However, in most cases MHRA licensing continues to apply to Northern Ireland, as does NICE guidance (post-licence). As a result of this, market access in Northern Ireland is also covered by the ILAP.

THE ILAP CRITERIA

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

- the condition is life-threatening or seriously debilitating
- there is a significant patient or public health need

2. The medicinal product fulfils one or more of a specific area

The areas are:

a) innovative medicine such as an advanced therapy medicinal product (ATMP) or new chemical or biological entity or novel drug device combination

b) medicines being developed in a clinically significant new indication for an approved medicine

c) medicines for rare disease and/or other special populations such as neonates and children, elderly, and pregnant women

d) development aligning with the objectives for UK public health priorities such as the Chief Medical Officer, Department of Health and Social Care (DHSC) or Life Sciences Sector Deal (including those in Devolved Administrations, where appropriate)

For this criterion, the applicant should indicate which area(s) the product belongs to. Depending on the area, you must provide the following evidence:

a) a full regulatory description of the product so that its status can be determined (e.g., name of drug substance, pharmaceutical form, route of administration, mechanism of action)

b) a description of the new indication in the context of the patient group, including the novelty of the proposal

c) a description of the use of the medicine in a particular special population

d) a description of where and how the product will fulfil public health priorities

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

This is the verbatim:

You must provide a summary of how patients are likely to benefit from the product or indication coming to market, including proposed improved efficacy or safety, contribution to patient care or quality of life, as compared to alternative therapeutic options. This should be based on evidence from the applicant with the product.

The claims can be supported either by data from valid non-clinical models of the condition or if justified extrapolated from another relevant model.

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

MHRA STATEMENT ON APPROVALS

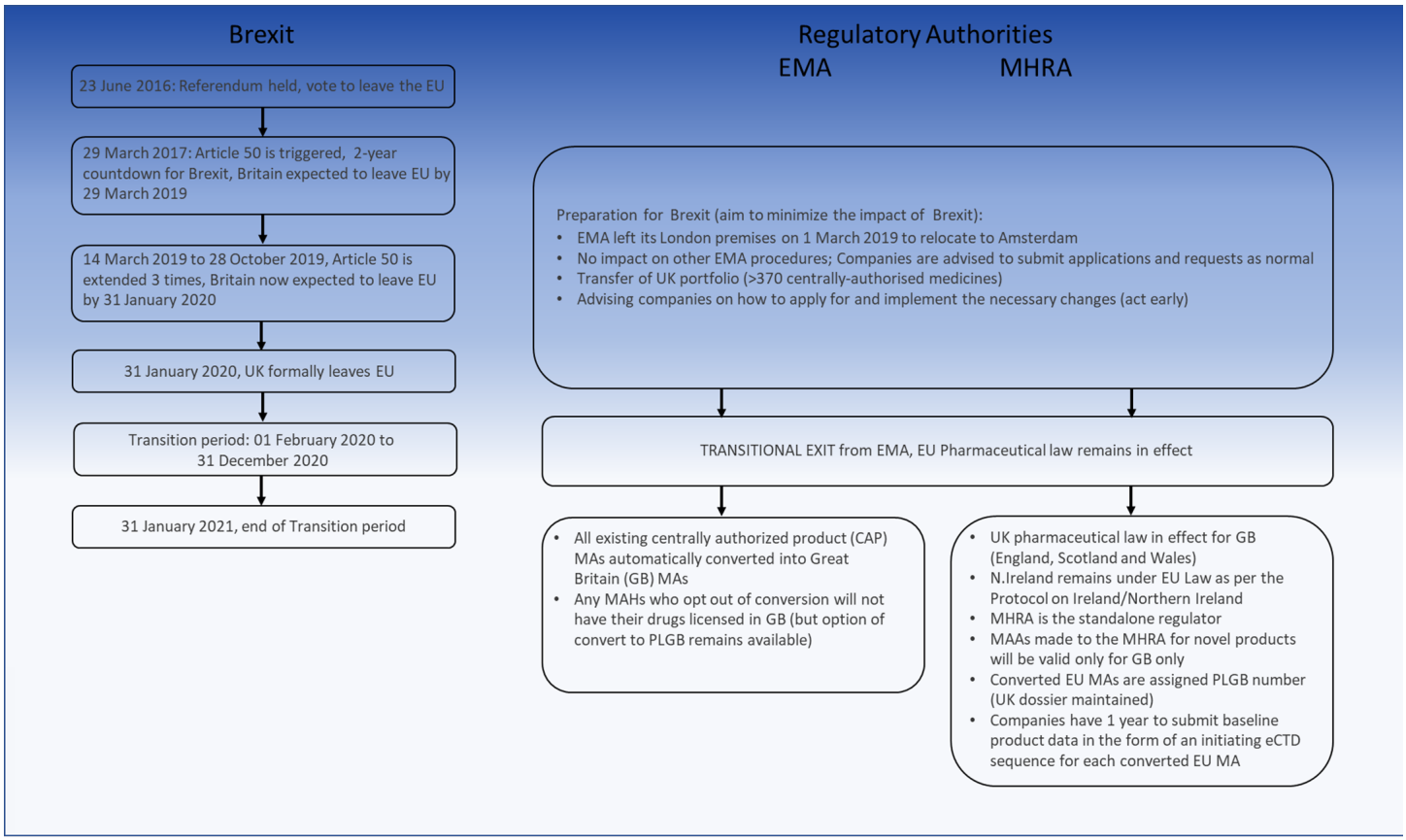
The MHRA has developed innovative and expedited licensing routes, and there are several routes to obtain a marketing authorisation in the UK, Great Britain, or Northern Ireland. The new pathways aimed at accelerating the time to market and facilitating patient access to medicines, such as the ILAP, a novel pathway formed by the MHRA, NICE, SMC, and the AWTTC to constitute a unified and seamless path for patient access to innovative new technologies in the UK also help ensure that the MHRA remains at the forefront of medicine regulation.

The ILAP is positioned as a model to consider for accelerated market access. Organisations could gain advantage in securing regulatory, reimbursement, and scientific advice from early in the clinical development path; time and resources could be saved that may otherwise have been expended in achieving market access. The ILAP could be especially important for smaller companies with less strategic support.

CONCLUSION

In the UK and Europe we are experiencing a period of intense change within our profession, as well as change across the regulatory landscape in general. Certara is well-placed to provide expert guidance and support in these fields. If you would like to discuss any of the points we raise above, or any other matter in relation to your development and registration strategy, please do feel free to get in touch.

THE IMPACT OF LEAVING THE EU ON REGULATION IN THE UK



About Certara

Certara accelerates medicines using proprietary biosimulation software, technology and services to transform traditional drug discovery and development. Its clients include more than 2,000 biopharmaceutical companies, academic institutions and regulatory agencies across 62 countries.

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