



Transition of Pharmaceutical Regulations: The New Regulatory Era after Brexit

**Trivedi Ankit^{1*}, Deshpande Shrikalp², Zaveri Maitreyi³,
Jain Praveen Kumar⁴ and Kolhe Kiran¹**

¹AGM, Regulatory Affairs, Amneal Pharmaceutical Ltd., Ahmedabad, Gujarat, India.

²K. B. I. P. E. R., Gandhinagar, Gujarat, India.

³Department of Regulatory Affairs, Head of Department of Regulatory Affairs, K.B.I.P.E.R., Gandhinagar, Gujarat, India.

⁴Regulatory Affairs, Amneal Pharmaceutical Ltd., Ahmedabad, Gujarat, India.

Authors' contributions

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ABSTRACT

Aims: The current research paper describes the regulatory changes in different pharmaceutical sectors, which are affected after the Brexit and build new guidelines that were derived from the Medicines and Healthcare Products Regulatory Agency (MHRA).

Study Design: Retrospective and concurrent review were employed to get idea regarding the regulatory changes in various pharmaceutical sectors that took place after dissimilation of Europe and Britain.

Place and Duration of Study: The present study was carried out at Amneal Pharmaceutical Ltd., from January 2021 to April 2021.

Methodology: On January 1, 2021, the MHRA had published a library of new guidance that applied as the transition period came to an end. This guidance covers the various sectors of pharmaceuticals like Clinical trials, medical devices, Importing and Exporting of pharmaceuticals, Legislation, New licensing, Pharmacovigilance and Pediatrics, which are affected due to Brexit.

Results: The MHRA laid out the future BRITAIN requirements for registering clinical trials, legal representation and importing Investigational Medicinal Products (IMPs) after the end of the Brexit, Pediatric Investigation Plan (PIP) must be included in an application for BRITAIN marketing authorization (MA). Change in Licensing procedure and the Innovative licensing and access Pathway (ILAP) provides opportunities for enhanced regulatory and other stakeholder input, including interactions with National Institute for Health and Care Excellence. Early Access to Medicines Scheme (NICE.EAMS) providing access to unlicensed, promising treatments to patients who have life threatening or rare disease indications.

Conclusion: To ensure the new approach builds on our previous success and exploits the opportunities that arise from Brexit, the industrial strategy should adopt a sophisticated supply chain view to develop an empirical base for pragmatic, joined up policies to help pharmaceutical sector grow. These policies and support will drive the BRITAIN's pharmaceutical sector in a Post-Brexit era.

Keywords: European Union; medicines and healthcare products Regulatory Agency; brexit; clinical trials; pediatric investigation plans; licensing of medicinal products; early patient access, orphan medicinal products; importing and exporting.

1. INTRODUCTION

The European Union (EU) is a political and economic union of 28 member states that are located primarily in Europe. The EU has developed an internal single market through a standardized system of laws that apply to all members in only those matters, where members have agreed to act as one. EU policies aim to ensure the free movement of people, goods, services, and capital within the internal market, enact legislation in justice and home affairs and maintain common policies on trade, agriculture, fisheries, and regional development. Some of the member states are Denmark, France, Germany, Poland, Spain, etc.

On December 24, 2020, the EU and BRITAIN finally agreed to a trade deal. Annex Technical Barriers to Trade (TBT-2) of this trade deal contains the agreed provisions for medicinal products. The agreement applies to the medicinal products for humans including marketed biological and immunological products for human and veterinary use:

- Advanced therapy medicinal products
- Active pharmaceutical ingredients for human or veterinary use
- Investigational medicinal products

For the pharma industry, like many others, the reality of a post-Brexit world is a daunting one. Despite months of negotiations, the

repercussions are still yet to be seen and COVID-19's impact on the economy and healthcare system has exacerbated the challenges ahead. The pharmaceutical sector is the third-largest industry in the BRITAIN and, according to the Association of the British Pharmaceutical Industry (ABPI), adds £13.8 billion (\$18.8 billion) to the British economy per year (gross value added) on average. Across the country, pharmaceutical companies have been working out how to unravel decades of EU integration. The industry relies to a large extent on harmonized procedures in the EU, cross-border processes, goods and value chains; Brexit will certainly cause waves.

This may result in additional costs for companies in the sector and concerns over patients' access to healthcare.

Key implications include:

- Mutual recognition of Good Manufacturing Practice (GMP) inspections. Unfortunately, this agreement is not a mutual recognition agreement (MRA) and does not include removing the requirement for re-testing of the product made in the Britain on importation into the EU, and vice versa. For political reasons, this requirement may not be removed for several years, if ever.

- Regulatory cooperation: Notable absences from the trade agreement include any mention of herbal medicinal products or medical devices. Also absent is any arrangement for a two-way alert system or pharmacovigilance information sharing.

Legislation
Licensing
Pharmacovigilance
Pediatrics

So, this article describes the major changes made in MHRA guidelines after dissimilation of Britain and Europe.

From January 1, 2021, the Medicines and Healthcare products Regulatory Agency (MHRA) has published a library of new guidance that applied as the transition period came to an end. This guidance covers the following areas:

Clinical trials
Devices
Importing and exporting
IT systems

1.1 Aims

To report and describe the Regulatory changes in different areas which are affected pursuant to the Brexit and to detail out the new guidelines that were derived from the Medicines and Healthcare products Regulatory Agency [MHRA].



Fig. 1. The Brexit Map

2. METHODOLOGY

A retrospective and concurrent review was undertaken to document the regulatory changes that took place after dissimilation of Europe and Britain. Internet data bases were searched including Google, Google scholar and Yahoo. The search words that were used included Brexit, Advancement of Brexit, European Union, Medicines and Healthcare products Regulatory Agency, Brexit, Clinical trials, Pediatric investigation plans, Licensing of medicinal products, Early patient access, Orphan medicinal products, Importing and exporting. Twenty three references were identified which were used to write the article.

3. RESULTS AND DISCUSSION

3.1 Clinical Trials

Brexit has introduced significant uncertainty over the future of clinical trials and the Britain's ability to collaborate with and engage in European trials. On September 1, 2020, the MHRA laid out the future BRITAIN requirements for registering clinical trials, legal representation, and importing Investigational Medicinal Products (IMPs) after the end of the Brexit transition period at the end of 2020. New rules and regulations around clinical trials and the approval of new medicines could boost the competitiveness and productivity of pharmaceutical companies that test and release drugs in the BRITAIN. Rather than being governed by the EU Clinical Trials Directive, the BRITAIN can refine its own national clinical trials regulation. This could speed up the release of new drugs into the market, ultimately benefiting the patient. The BRITAIN has looked to form alternative partnerships to ease the separation implications. For example, the MHRA has joined the Australia, Canada, Singapore, and Switzerland Consortium. When the MHRA joins this regulatory agency in January 2021, the newly re-branded Access Consortium will cover 145 million people and open the BRITAIN's access to lucrative markets.

3.1.1 Sponsor or legal representative

From 01 January 2021, either the sponsor or the legal representative of a clinical trial must be established in the BRITAIN or in a country on the approved country list, which includes EU/European Economic Area (EEA) Member States.

EU law requires that the clinical trial sponsor or a legal representative must be established in the EU. If an ongoing clinical trial is in the EU/EEA, but the sponsor or its legal representative is based in the BRITAIN, then the sponsor must submit a substantial amendment to the relevant EU/EEA regulatory authorities to update the information about the legal representative established in the EU/EEA [1].

3.1.2 MHRA submission portal

The new MHRA Submission Portal should be used for regulatory applications submitted to the BRITAIN, including but not limited to:

- All pharmaceutical companies involved in making regulatory medicinal product submissions and vigilance activities for the BRITAIN (Great Britain [GB] and Northern Ireland)/GB licenses
- All medicines clinical trial sponsors wishing to make clinical trial submissions (initial applications, substantial amendments, end of trial notifications, and developmental safety update reports) to the MHRA [2].

3.1.3 Investigational Medicinal Products (IMPs)

IMPs imported into GB from outside of the BRITAIN that have been Qualified Person (QP) certified in a listed country will not require recertification in GB. Starting on 01 January 2022, IMPs that are QP released in a listed country outside of the BRITAIN will require a BRITAIN Manufacturing and Import Authorisation holder to put in place an assurance system to ensure the IMPs have been certified by a QP in a listed country before releasing to trial sites [3].

Clinical trials involving EU/EEA sites with only BRITAIN-based IMP release sites will need to include the EU/EEA IMP release sites via submitting substantial amendments to the relevant EU/EEA regulatory authorities [1].

3.1.4 Registration of clinical trials and publication of summary results

Existing and established international registers, such as the International Standard Randomized Controlled Trial Number (ISRCTN) registry or ClinicalTrials.gov, should continue to be used. For trials involving both Britain and EU sites, a record in the EU Clinical Trials Register will exist (other than for adult Phase I trials).

In the BRITAIN, any favorable 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 the recruitment of the first participant.

The time frame for publishing the summary of results is within six months of the end of the trial for pediatric trials or within one year for non-pediatric trials. Sponsors should publish the summary results within these time frames in the public register (or registers) where the clinical trial has been registered. The clinical trial summary report does not need to be submitted to the MHRA. However, a short confirmatory email must be sent to CT.Submission@mhra.gov.Britain once the results information has been uploaded to the public register, and a link should be provided. If a clinical trial is not on a public register, then summary results should be submitted to the MHRA [4].

3.2 Paediatric Investigation Plans (PIPs)

The legal requirements for Britain Paediatric Investigation Plans (PIPs) from 1 January 2021 are set out in the Human Medicines Regulations 2012, as amended by the Human Medicines Regulations (Amendment etc.)(EU Exit) Regulation 2019.

Under the Human Medicines Regulations, results from an agreed PIP must be included in an application for Britain Marketing Authorisation (MA) for a Britain application for a relevant medicinal product which is an initial marketing authorisation for the purposes of global marketing authorisation, or an application for a new indication, new pharmaceutical form or new route of administration in relation to a product which is already subject to an existing BRITAIN MA. This requirement can be waived or deferred – if so, the MA application has to contain a decision granting the deferral or waiver (including a decision from the European Medicines Agency granting a class waiver and confirmatory letter that the medicinal product falls under the class waiver). The Britain government guidance, Format, and content of applications for agreement or modification of a Paediatric Investigation Plan and request for waivers or deferrals and concerning the operation of the compliance check from 1 January 2021, provides detailed information on the format and content for

submissions relating to PIPs, including information on what should be provided in an application for marketing authorisation.

The requirement to include results from an agreed PIP does not apply to certain applications, being applications for generic medicinal products, certain medicinal products that do not qualify as generic, similar biological medicinal products and products in well-established medicinal use.

The purpose of a PIP is to ensure that there is necessary data supporting that the medicine or proposed new indication, pharmaceutical form or route or administration will be safe for use in children. Accordingly, regulation 50B of the Human Medicines Regulations 2012 (as amended) states that a PIP must:

- a. *specify the timing and measures proposed to assess the safety, quality and efficacy of a medicinal product in the paediatric population; and*
- b. *describe any measures to adapt the formulation of the medicinal product so as to make its use more acceptable, easier, safer or more effective for different subsets of the paediatric population.*

After 1 January 2021, Britain PIPs will be submitted to the MHRA. The requirements for scientific content and assessment will be kept in line with the EMA guidance documents, as confirmed in the BRITAIN government guidance, Procedures for Britain Paediatric Investigation Plan (PIPs) from 1 January 2021 (1 September 2020). It is also confirmed that the BRITAIN will follow the principles as published in the European Commission's Guideline on the format and content of applications for agreement or modification of a paediatric investigation plan and request for waivers or deferrals and concerning the operation of the compliance check and on criteria for assessing significant studies.

If a Britain PIP is required, it needs to be submitted to the MHRA no later than upon the completion of the human pharmacokinetic studies in adults, according to regulation 50B of the Human Medicines Regulations 2012 (as amended).

When a PIP application is submitted to the MHRA, the information should be provided on whether there is:

- An agreed EU-PIP, the
- Paediatric Committee (PDCO) opinion, and supporting documentation included
- An ongoing EU-PIP assessment and its timeline in the PDCO assessment cycle (ie, Day 30, 60, clock stop, Day 90, or 120)
- Any current scientific divergence between the submitted PIP application and the EU-PIP

The MHRA will aim to maintain alignment with a positive PDCO opinion if one is reached before the MHRA assessment is completed. However, divergence could occur, and a number of BRITAIN factors need to be considered, such as:

- Unmet BRITAIN pediatric needs.
- The incident of the disease in the BRITAIN population.
- The relevance of the scientific argument by EMA/PDCO in the summary report to the BRITAIN pediatric population.
- Any additional safety or efficacy concerns for the BRITAIN population.
- The feasibility of performing the proposed pediatric studies in the BRITAIN only.

For new BRITAIN-PIP submissions where there is no corresponding European Union Paediatric Investigation Plan (EU-PIP) submission or the Paediatric Committee (PDCO) opinion is negative, a full assessment of the United Kingdom Paediatric Investigation Plan (BRITAIN-PIP) is required. If the applicant chooses to submit to the MHRA and has a negative Paediatric Committee (PDCO) opinion, the applicant should consider incorporating changes to the United Kingdom Paediatric Investigation Plan (BRITAIN-PIP) for the elements that received a negative PDCO assessment [5].

3.3 Licensing of Medicinal Products

3.3.1 Existing Marketing Authorisations (MAs)

On 01 January 2021, all existing, centrally-authorized MAs in the EU have been automatically converted into BRITAIN MAs effective in GB only and issued with BRITAIN MA numbers. To support the ongoing regulation of these converted EU MAs, by 31 December 2021, marketing authorization holders (MAHs) need to submit essential baseline data to the MHRA in the form of an initiating electronic Common

Technical Document (eCTD) sequence together with other MA-specific information for each converted EU MA [6].

The MAH for a Britain MA must be established in the Britain (GB or Northern Ireland) or in the EU/European Economic Area (EEA). For medicinal products with an EU/EEA MA, a MAH established in the Britain will need to be replaced with a MAH established in one of the remaining countries of the EEA. This change in MAH requires a MA transfer application from a Britain - based MAH to a different legal entity established in the EEA [7].

3.3.2 The European Commission Decision Reliance Procedure (ECDRP)

All existing Converting Centrally Authorised Products Marketing Authorisations (CAP Mas) have been automatically converted into BRITAIN MAs effective in Great Britain (only) and issued with a BRITAIN MA number on 1 January 2021. These BRITAIN MAs are referred to in this guidance as "converted EU MAs". As a result of the implementation of the Northern Ireland Protocol, existing CAPs will remain valid for marketing products in Northern Ireland. From the regulatory perspective, Northern Ireland will remain covered by the European Medicines Agency's (EMA) centralized procedure (CAP) and could be part of the Decentralised procedure / Mutually Recognised Procedure (DCP/MRP) procedure as Concerned Member State (CMS).

Although the MHRA will remain responsible for the monitoring and enforcement in this territory. For the new application, you still could add Northern Ireland (NI) as a CMC but wouldn't have access to the GB market with the same MA as it was previously.

In order to reduce the impact and speed up access to the critical MHRA implemented a couple of piggyback strategies for the transition period.

Until January 1st, 2023, when determining an application for a Great Britain Marketing Authorisations (MA), the MHRA may rely on a decision taken by the European Commission (EC) on the approval of a new MA in the centralized procedure.

For the products that have been submitted via centralized procedure for review by the European Medicine Agency (EMA) there are 2 potential

routes in adding the new BRITAIN marketing authorization:

- Standalone GB application: Parallel national market authorization application Assessment in which the manufacturer/future Marketing Authorization Holder (MAH) applies to the MHRA in parallel with EMA Centrally Authorized Product (CAP).
- Reliance Route in which the manufacturer can wait until the CHMP has issued a positive opinion before applying to the MHRA for a Britain marketing authorization.

GB national application requirements and procedure will remain the same, but we should discuss how your market access to the BRITAIN could be made faster with Reliance Route.

The intended operation of the ECDRP is a submission of the Marketing Authorisation Application (MAA) to the MHRA immediately on receipt of a positive Committee for Medicinal Products for Human Use (CHMP) opinion, although applications can be submitted any time after the approval of a European Union Marketing Authorisation [8,9].

3.3.3 The Decentralized and Mutual Recognition Reliance Procedure (MRDCRP)

The decentralised and mutual recognition reliance procedure (MRDCRP) describes a new possible route to BRITAIN marketing authorisation (MA) that relies on approvals through the European decentralised (DC) and mutual recognition (MR) procedures, to grant marketing authorisation in the BRITAIN or GB. The MRDCRP is not available to products with MAs in the EU Member States granted only through national procedures [10].

3.3.4 Unfettered access from Northern Ireland

Applicants may seek recognition in GB for a MA approved in Northern Ireland. This route is available for MAs approved in Northern Ireland via EU centralized, mutual recognition, or decentralized procedures or through the national procedure if the MAH is established in Northern Ireland and the product is distributed from Northern Ireland to GB [11].

3.3.5 The 150-day Assessment for National Applications

Guidance on 150-day assessment for national applications for medicines describes a new national accelerated assessment route for Marketing Authorisations (MAs) in the BRITAIN. Under this process, the MHRA will evaluate a BRITAIN MA application and reach an opinion within 150-days after submission of the application. The application route is available for new active substances, biosimilars and existing active substances.

For new active substances, biosimilars and existing active substances, the guidance provides a description of the content and format of the documents that will lead to successful applications/dossier submission. These guidelines include common technical modules 2-5 (CTD) and a Britain specific CTD module 1, the summary of product characteristics, patient information leaflet and active substance master file if applicable. Applications must also include a cover letter. The cover letter should detail any further intentions to seek orphan status or an MA under exceptional circumstances, as applicable. Applications should be submitted via the MHRA Submission Portal.

For new active substances and biosimilar products, the guidance advises:

- Applicants to communicate with MHRA prior to submission, informing the MHRA of the intended date of dossier submission. Additionally, should state if the application is intended for Britain or GB only or NI only.
- Applicants should inform the MHRA of the pre-submission meeting and issues that they would like to raise during the meeting. The pre-submission meeting offers the opportunity to discuss Britain compliance checks for the Paediatric Investigation Plan (PIP) and crucially may offer the opportunity to enhance joint discussions with the National Institute for Health and Care Excellence (NICE)

For existing active substances, applicants should refer to the MHRA guidance on Reference Medicinal Products for applications made only to GB. They are also advised to consult any MHRA product-specific bioequivalence guidance for applications made only to GB.

The MHRA also offers pre-submission meetings to discuss topics such as consideration for orphan MA, conditional MA, MA under exceptional circumstances, arrangements for a BRITAIN-PIP compliance check, etc. The pre-submission meeting may offer the opportunity to enhance joint discussion with National Institute for Health and Care Excellence (NICE) regarding the Health Technology Assessment (HTA) evaluation process [12].

3.3.6 Rolling review

The rolling review procedure is a new route for marketing authorisation (MA) that aim to streamline the development of novel medicines. MA applications for any new active substance, based on a “full dossier”, including biological products, are eligible for the route. Similar biological applications, i.e., biosimilar products, are also eligible.

The rolling review is a new route for Marketing Authorization Application (MAAs), where an applicant for a MA submits increments of the eCTD dossier for pre-assessment by the MHRA rather than as part of consolidated full dossier submission. This process is a modular approach to submission and evaluation. The quality, non-clinical, and clinical data may be submitted separately or jointly, depending on individual circumstances and/or data availability.

The rolling review is intended to reduce the risk of failure at the final phase by offering periodic regulatory interaction and advice and may be integrated with the Target Development Profile (TDP) to provide a clearer pathway for the development of innovative medicines [13].

3.3.7 Conditional Marketing Authorization (CMA)

The MHRA will introduce a national Conditional Marketing Authorisation (CMA) scheme for new medicinal products for unmet medical needs in Great Britain from 1 January 2021. The EU, EEA and Northern Ireland will continue to submit to the EMA under the centrally Authorised Procedure as before. Examples would be for serious and life-threatening diseases where no satisfactory treatment methods are available or where the product offers a major therapeutic advantage.

The MHRA may grant a CMA where comprehensive clinical data are not yet complete, but it is judged that such data will

become available soon. The MAA must still contain adequate safety and efficacy evidence to enable the MHRA to conclude a positive risk-benefit balance of the medicinal product.

Applicants wishing to submit an application for a CMA to the MHRA should state their justification for a CMA, clearly indicating what clinical studies are underway and when comprehensive clinical data will become available. The designation of a product eligible for a CMA by the EMA or another jurisdiction may be taken into account by the MHRA, but the final decision on the eligibility of the product for the GB scheme will rest with the MHRA.

Eligibility for a CMA will be determined by the MHRA at the time of MAA assessment. After assessing the MAA dossier, the MHRA will determine whether to approve the application and grant a CMA or whether the risk-benefit ratio is negative and reject the application. CMAs will be valid for one year and will be renewable annually [14].

3.3.8 MAs 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 the collection of full information is not possible or is unethical.

The scheme has the same eligibility criteria as the EU scheme and is intended for medicinal products that fulfill an unmet medical need. Examples would be for serious and life-threatening diseases where no satisfactory treatment methods are available or where the product offers a major therapeutic advantage. 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.

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

The designation of a product as being eligible for an exceptional circumstances scheme by the EMA or another jurisdiction may be taken into

account by the MHRA, but the final decision on the eligibility of the product for the GB scheme will rest with the MHRA.

3.4 Innovative Licensing and Access Pathway (ILAP)

ILAP was announced in December and launched at the start of the year to accelerate the development and access to promising medicines and is geared toward medicines that are in the early stages of development. The pathway, part of the BRITAIN's plan to attract life sciences development in the post-Brexit era, features enhanced input and interactions with MHRA and other stakeholders including the National Institute for Health and Care Excellence (NICE) and the Scottish Medicines Consortium (SMC).

The innovation passport designation is the first step in the ILAP and triggers the MHRA and its partner agencies to create a target development profile (TDP) document to chart out a roadmap for regulatory and development milestones with the goal of early patient access in the BRITAIN. Other benefits of ILAP include a 150-day accelerated assessment, rolling review and a continuous benefit risk-assessment.

The ILAP aims to accelerate the time to market, facilitating patient access to medicines such as new chemical entities, biological medicines, new indications, and repurposed medicines. The ILAP provides opportunities for enhanced regulatory and other stakeholder input, including interactions with NICE.

The developers are required to apply for the Innovation Passport to enter the ILAP, and the eligibility criteria for the passport are:

- The condition is life-threatening or seriously debilitating, or there is a significant patient or public health need.
- The medicinal product fulfills one or more of the following areas:
 - Innovative medicine such as an advanced therapy medicinal product (ATMP), new chemical entity, new biological entity, or novel drug-device combination.
 - The medicine is being developed in a clinically significant new indication.
 - Medicine for rare diseases and/or other special populations such as neonates, children, elderly, and pregnant women.

- Development aligns with the objectives for BRITAIN 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).

- The medicinal product has the potential to offer benefits to patients:
 - 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, if available, clinical data in a relevant patient population can be provided. If available, applicants are strongly encouraged to include the views from patients or patient organizations around the benefits of a product in their evidence.

To maximize the benefits of ILAP, applicants are encouraged to apply for entry very early based on non-clinical data. Products that are towards the end of their development program are generally not suitable for the ILAP [15].

3.5 Project Orbis

With the BRITAIN leaving the European Medicines Agency (EMA) regulatory process in late 2020 as part of Brexit, the BRITAIN Government and the Medicines and Healthcare products Regulatory Agency (MHRA) rolled out new approaches for the commercialization of pharmaceuticals. One central tenet was to establish the BRITAIN as an attractive market with the potential for fast marketing authorization pathways, and a keynote program was the Britain joining Project Orbis.

Project Orbis is a global, collaborative, program launched by the FDA Oncology Center of Excellence (OCE) in 2019, which aims to speed up patient access to innovative cancer treatments through a framework of concurrent regulatory submission and review. Today, there are six Project Orbis Partners (POPs): Australia (TGA), Canada (Health Canada), Singapore (HSA), Switzerland (Swissmedic), Brazil (ANVISA) and most recently the United Kingdom

(MHRA). While FDA serves as the coordinator for application selection and review, each country remains fully independent on its final regulatory decision.

From a patient access point of view, Project Orbis has received significant positive press however an open question remains on whether access timelines are truly expedited in all markets.

It is worth noting, however, that whilst some national routes are dependent on other regulatory body processes (e.g., EC Decision Reliance Procedure) the standalone MHRA process is the National procedure, which is expected to take 150 days for marketing authorization. Comparing this to the Project Orbis timelines of 5 to 6 months, MHRA timelines are projected to lead to faster BRITAIN access than engaging in Project Orbis.

Regardless of the type of Project Orbis submission, to be eligible for Project Orbis in the BRITAIN, the drug under consideration must also qualify for the national Innovative Licensing and Access Procedure (ILAP). While the manufacturer does not necessarily have to have engaged with the ILAP prior to requesting inclusion in Project Orbis with the BRITAIN as a POP, the MHRA will arrange an "Innovation Passport" meeting to confirm eligibility. Reversing this rationale, manufacturers who do not want to engage the BRITAIN in Project Orbis are likely to remain eligible for, and gain the advantages of, other innovative access routes into the BRITAIN.

While considering the advantages and risks of Project Orbis, the second "Access Consortium" international route must also be considered, defined as work-sharing procedures between national regulators. Notably, this consortium includes all Project Orbis markets, excluding the US and Brazil, and not restricted to oncology indications. While there may be synergies through this approach, offering a more attractive commercial opportunity than to the BRITAIN market alone outside the EU, the benefits of this route will likely be dictated by manufacturer engagement and submission [16].

3.6 The Early Access to Medicines Scheme (EAMS)

EAMS is recognised by all parties as having many benefits in providing access to unlicensed, promising treatments to patients who have life-

threatening or rare disease indications. However, while the initial framework for applying for EAMS is now in place, issues affecting the uptake and implementation of the scheme continue to be the subject of much discussion. EAMS is a three-step voluntary evaluation process consisting of Step I, the Promising Innovative Medicine [PIM] designation; Step II, the Scientific Opinion and Step III, Commissioning in the NHS. Applicants can only apply for an EAMS Scientific Opinion for therapies with Phase III data (Phase II data in exceptional circumstances). The event participants discussed why providing this type of data is going to be impractical for many therapies to treat rare disease indications. There was a suggestion from medical research charities and industry that for these types of disease, robust Phase II data should be an accepted standard for submission in a Scientific Opinion application.

The question of funding for applying and running the scheme, as well as providing therapies free of charge, was also raised several times by industry experts. They stated that the PIM designation was affordable while applying for Scientific Opinion would require very careful review as to its cost-effectiveness, especially for many Small and Medium Enterprise (SMEs).

Payment models, similar to those utilised in Japan for expensive to manufacture cell therapy treatments, were mooted as one possible solution. Another avenue discussed to resolve this issue would be to have government funding available for EAMS application, and to review Britain Government funded reimbursement models based on the success of the therapy in EAMS. The availability of Britain Government funding for EAMS is supported by both the Association of the British Pharmaceutical Industry (ABPI) and the Bioindustry Association (BIA) as a way forward and they are calling for a one-year on joint review of the scheme to appraise its first year and potentially review its functioning, including funding options.

Industry experts and medical research charity representatives highlighted that in Step III EAMS commissioning by NHS England, the process for National Institute for Health and Care Excellence (NICE) evaluation and timelines for commissioning requires greater clarity to allow companies to fully evaluate the utility of EAMS. NHS England's view was that these issues would be resolved during the coming year when the first treatments have been through EAMS. The MHRA also encouraged industry to engage with

the scheme and provide feedback on their experiences so that EAMS would provide the intended patient benefit. To maximise the potential of EAMS, the ABPI and the BIA continue to call for central government reimbursement, as well as greater clarity on the commissioning process, to ensure both patients and industry benefit from the development of these ground breaking therapies.

The EAMS was established in 2014 based on Article 5(1) of Directive 2001/83/EC (named patient use) and aims to give patients with life-threatening or seriously debilitating conditions access to medicines that do not yet have a MA when there is a clear unmet medical need. It also aims to balance the interests of stakeholders, including patients, industry, clinicians, and the National Health Service (NHS) [17-19].

3.7 Orphan Medicinal Products

The most obvious difference between the EU and the new Britain system is that there is no pre-authorisation orphan designation in Great Britain (or the Britain, although a Britain-wide orphan marketing authorization(**MA**) can only be considered in the absence of an EU orphan designation, which will be extremely uncommon).

This could be seen by some as an advantageous simplification of the procedure, but in reality, it provides more uncertainty to sponsors and dependence on the EU, as developers will not know who else is developing similar products for the same orphan condition without relying on the more transparent and open EU system. Indeed, in Great Britain, sponsors will enter the race to be the first to obtain an MA for their orphan medicinal products with blinkers and the European Commission Register of Orphan Medicinal ("EC Register") will be the only source available to them to understand what the competitor landscape looks like at any given point in time.

The Britain equivalent of the EC Register is now a mere list of granted orphan marketing authorization, together with a list of expired orphan registrations. The database, published and kept up to date by the MHRA, is rudimentary consisting of a list of orphan registered products in alphabetical order by trade name. The MHRA list does not fulfil the same objective as the EC Register, which was set up to enable an easy

and unequivocal tool for the identification of medicines eligible for incentives. To the extent that products are added to the Britain list once they are authorised (in the absence of orphan designation prior to the application for the MA), the Britain list is a mere compilation of products that have market exclusivity, which does nothing to enhance transparency and openness.

Given the residual and purely testimonial purpose of the BRITAIN list, the Britain legislature must have considered it unnecessary to retain the different ways in which a designated orphan medicinal product can be removed from the EC Register (Art. 5.12 of the EC Orphan Regulation). As a consequence, from 1 January 2021 MA holders of orphan medicinal products approved in Great Britain (or the BRITAIN) cannot voluntarily de-designate their products. This seemingly small change has important consequences that will create relevant differences between the Britain and the EU.

Firstly, an MA holder is no longer able to de-designate its product to add non-orphan indications while orphan market exclusivity (**OME**) exists for its Great Britain or BRITAIN product, forcing it to apply for a new MA, under a different brand, if it wants to commercialise its product for non-orphan indications.

Second and most importantly, an MA holder of an orphan medicinal product is no longer able to choose the preferred paediatric reward (the six-months extension of the Summaries of Product Characteristics (SPC) or two additional years of OME) when its product is both orphan designated and is protected by an SPC or a patent that qualifies for one at the relevant point in time. While in the EU it is commonly accepted that an MA holder of a product which is both orphan designated and protected by an SPC or a patent that qualifies for one can choose the most economically attractive paediatric reward, this is no longer possible in the BRITAIN. Having been left without the possibility of removing its product from the list of orphan medicines, and giving up part of the product's OME as a result, the MA holder of an active orphan medicinal product in Great Britain or the BRITAIN cannot opt for the six-months extension of the SPC while the 10 years of OME lasts. The only reward available for these products in the BRITAIN will be the extension of the orphan marketing exclusivity to 12 years [20].

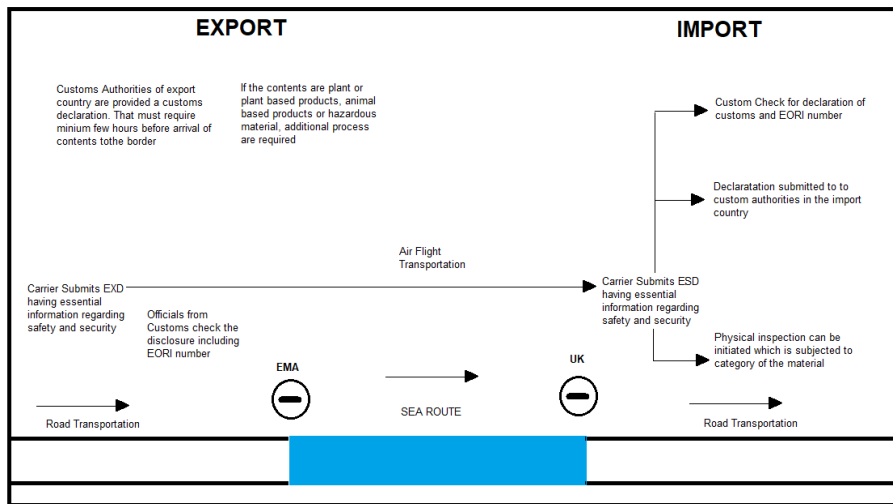


Fig. 2. An overview of the clearance process

3.8 Importing and Exporting

From 01 January 2021, to move goods (including medicinal products) across the EU-BRITAIN border, GB importers and exporters must have an Economic Operators Registration and Identification (EORI) number issued by the BRITAIN. EU importers and exporters must have an EORI number issued by an EU Member State. If a BRITAIN or GB authorized medicine is imported from a country on the approved country for import list (which includes all EU/EEA countries), the wholesaler must hold a wholesale dealer's license that authorizes import.

The license granted to a wholesaler before 01 January 2021 will continue to be valid. Thus, wholesalers with licenses that already import medicinal products from the EU/EEA to GB can continue to do so, provided that they notify the MHRA of their intention to continue to import medicinal products from a country on the list by 30 June 2021. They will need to nominate and name a Responsible Person import (RPI) in their license by 31 December 2022.

If a wholesale dealer does not already hold a license before 01 January 2021, they will need to apply for a license. The requirement to name an RPI on the license will apply immediately to all new license applications made from 01 January 2021, which cover the importation of medicinal products from a country included on the list. The RPI is required to implement a system for confirming the QP certification and independent batch release certification (for biological products) has taken place when importing products into GB from countries on the approved country for import list.

As in the case of Investigational Medicinal Products (IMPs) for medicinal products that only have batch release and quality control testing sites in the BRITAIN, new batch release and testing sites located in the EU/EEA will need to be established. Each batch of finished products must be certified by a QP within the EU/EEA before being released on the EU/EEA market [21-23].

4. CONCLUSION

To ensure the new approach builds on our previous success, and exploits the opportunities that arise from Brexit, the industrial strategy should adopt a sophisticated supply chain view to developing an empirical base for pragmatic, joined up policies to help sectors grow. These policies and business support will drive the BRITAIN's economy in a post-Brexit world. Regulatory decisions on medicinal products in the BRITAIN (with the exception of Northern Ireland) are no longer taken by the EMA, but by the MHRA as the 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 BRITAIN regarding the authorization of medicines and medical devices.

CONSENT

It is not applicable.

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

DISCLAIMER

The content used for this research to explore the overall Brexit impact in the field of Regulatory Affairs. There is absolutely no conflict of interest and we do not intend to use these contents as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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