WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

Navigating Post-Brexit Regulations: A Review of Drug Products and Medical Devices in the UK

Priyanka. Lukalapu[1], Alekhya.Lam[2*], Madhav. Vemireddy[3]

Students, Andhra university, Regulatory Affairs department, Visakhapatnam, 530003
Email; alekhya1.lam@gmial.com

ABSTRACT:

In the UK, the regulatory agency is called the Medical and Healthcare Products Regulatory Agency (MHRA). In the UK, the MHRA is in charge of regulating medications and medical equipment. The United Kingdom's departure from the European Union is referred to as Brexit. Prior to Brexit, the European Medicines Agency (EMA) was in charge of the regulations governing the marketing of pharmaceuticals and medical devices. Thus, the Agency for the Regulation of Medical and Healthcare Products was established. The four nations that comprise the United Kingdom are England, Scotland, Wales, and Northern Ireland. The Medical and Healthcare Products Regulatory Agency website portal was used to complete the licensing process for drug marketing. research. The applicant uses the MHRA portal to submit the documents electronically in Common Technical Document format. The MHRA has established a number of new pathways for the examination of marketing authorization for pharmaceuticals and medical devices. The UK created the Yellow Card program to gather direct patient data about medication side effects on the Medical and Healthcare Regulatory Products Agency website. This data is then used to support research on novel drugs and medication safety.

Key words: Medical and Healthcare Products Regulatory Agency (MHRA), United Kingdom (UK), European Union (EU), Brexit, electronic CTD, Yellow Card

INTRODUCTION:

There are twenty-eight countries that make up the European Union (EU). Originally constructed on the remains of the Second World War, it served to put an end to decades of hostilities and foster state-to-state financial cooperation. The European Economic Community (EEC), founded in 1973, included the UK as a member state. Later, in 1993, the EEC was renamed the European Union (EU) in an effort to improve fiscal cooperation. Since the outset, the UK has never been close to the EU. It did not take part in the Schengen agreement and has the pound sterling as its official currency.

The Schengen Agreement is a treaty that the European Union signed on June 14, 1985, that addresses the progressive removal of internal borders in Schengen, a small village in Southern Luxemburg on the Moselle River, between the five member countries of Europe: Belgium, Germany, France, Luxemburg, and the Netherlands. In the British political arena, opponents of the Schengen concept have always existed, and their numbers grew after the 2008 financial crisis. When David Cameron was prime minister in 2012, he announced that an election will be held to determine whether the UK should stay in the EU.

On June 23, 2016, the UK held the referendum as promised by him, but he resigned before the results were made public. Later, on March 29, 2019, the Brexit proposal was made; however, on January 31, 2020, it actually transpired. Following Brexit, the UK created the Medical and Healthcare Products Regulatory Agency (MHRA), which is its own regulatory body. After the United Kingdom left the European Union, some modifications were made to its legal system and administrative practices. The UK has altered its legislation in a number of ways from those of the EU.

APPLICATION OF LICENCE:

In order to file a marketing application for the sale of a new drug or medical device, applicants must first log in to the MHRA portal. They must then submit the cover letter and the eAF (electronic application form) in e-CTD format. Applications submitted without a cover letter and supporting documentation will not be accepted. The application submitted in Non-eCTD (NeeS) and eCTD is validated for the Pre-submission Checklist. Prior to filing an application through the MHRA portal, applicants must obtain a Product license (PL) number. The sections of the Pre-submission checklist for the application form consist of:

Section 1: Type of Application

Section 2: Marketing Authorisation Application Particulars Section

Section 3: Other Marketing Authorisation Applications Section

Section 4: Annexed Documents

ACTIVE SUBSTANCE MASTER FILE (ASMF):

A marketing authorization application (MAA) or a marketing authorization variation (MAV) of a medicinal product must include the active substance master file (ASMF), which was previously known as the European Drug Master File (EDMF) and changed to the UK ASMF after Brexit. The MHRA requires the Active Substance Master File from each applicant. The goal of this ASMF is to protect the manufacturer's valuable confidential intellectual property.

In the UK, the Committee for Medicinal Products for Human Use (CMPU), which was formerly CHMP in the EU, recommends that the dossier be filed in an active substance master file. If the applicant makes any changes to the dossier, new and updated ASMFs must be submitted using the MHRA submissions portal. The Marketing Authorization holder must transmit both the Applicant part (AP) and the Restricted part (RP) using the Active Substance Master File.

- A cover letter, an additional access letter and a complete administrative information form.
- The Biographical information of the team head.
- The AP and RP's superior general executive summaries.

SUMMARY PRODUCT CHARACTERISTICS (SmPC):

The SmPC, which is a formatted summary of characteristics, includes information such as the drug's name, its composition both quantitatively and qualitatively, its pharmaceutical form with analytical data, specifications, therapeutic characteristics, pharmaceutical data, the name of the marketing authorization holder, the marketing authorization number, the first authorization date or resumption date, and the text's revision assignment. All of these details must be submitted to the MHRA portal using the SPC template in the correct format. The application will be rejected if the MA holder submits it without using this template. All that is required of the application is to update the template with the accurate date before forwarding it to the Medicines and Healthcare Regulatory Agency.

LICENSING REQUIREMENTS FOR DRUGS IN THE UK:

Application process: The MHRA consent portal is required to be used for all national drug approval applications submitted by the United Kingdom (England, Scotland, and Wales).

eCTD PL number in format: Before proposing the application, the applicant must get a pro product licence from the MHRA portal.

Current Master File for Substances: The MA holder bears the duty of ensuring that the dossier is submitted exclusively to ASMF.

Summary of Product Characteristics (SmPC): Just adding the relevant data to the SPC template is the only modification that need be made.

Providing a name that allows the medication to be sold: The MHRA carefully considers each request for a product name to make sure the proposed name allows the medication to be safe.

Fast-tracking the Market Authorization: Applications may be subjected to fast-tracking if there is documented critical medicine scarcity (DHSC) or supporting proof of benefit in a public health emergency.

Fee: Fees vary depending on the route of marketing authorisation assessment.

Registration time: 60-90 days

Device details:

- The Global Medical Device Nomenclature (GMDN) code;
- The device's class, such as Class I, Class IIa, IIb, or Class III;
- The Basic Unique Device Identification (UDI)
- Model/version data;
- Catalogue/Reference number;
- Name of the medical item (trade, brand, or proprietary name);
- Parameters such as MRI compatibility and latex sterility

- If appropriate, a copy of the Certification of Conformity Assessment (UKCA) or CE (Conformite Europeenne) UKNI (United Kingdom Northern Ireland CE marking) certificate

Fee: A 100–240 pound sterling legal fee is applied to each medical device registration application.

Time of registration: 12–18 months

Plant Inspection: Required

II. UK DRUGS MARKETING AUTHORIZATION PROCEDURES

1. A 150-day National Protocol

2. Continuous evaluations

3. A decentralized and mutually acknowledged mechanism for reliance

4. The unfettered access and decision reliance procedure of the European Commission.

1. National Procedure/150-Day Procedure:

This is the quickest route for obtaining a marketing permission. The MHRA reviews applications from the United Kingdom, Great Britain, and Northern Ireland in 150 days or less. There is a 60-day break during the 150-day process, and the initial evaluation is completed after 80 days. The applicant's "Info request" will be used to process first-phase concerns (RFI letters). The 60-day period is subject to certain exceptions. First, orphan medications are identified. Following the candidate's response, round two starts. The MHRA will work with the Commission on Human Medicines (CHM) to establish a "submission date" in order to expedite CHM interactions.

2. Rolling review:

Rolling review/rolling assessment expedites the Marketing Authorization process for appeals involving biological goods or biosimilars with "complete dossiers." The MHRA pre-assesses applicants' eCTD dossiers. Modularity lowers the chance of a final-phase failure. The evaluation of the first module begins right away and lasts for sixty days. A Module Assessment Summary (MAS) is given after the assessment cycle. The applicant can modify the Module Assessment Summary (MAS) by using the Module Assessment Summary. The final phase should take two months. On day 60, the MHRA sends out a Request for Information (RFI), and the candidates have 30 days to respond.

With final approval on Day 100, the cycle recommences on Day 61. The pre-submission meeting should be requested by the applicant in order to understand the product's features, target market, and modules. The applicants may ask for marketing authorization in the United Kingdom, Great Britain, or Northern Ireland. Under the modular approach, the quality data, non-clinical data, and clinical data may be given concurrently or separately based on the assessment team's availability and the specific circumstances. Ninety days before they finally capitulate, the final batch of candidates consults the MHRA.

At this point, the applicant, who might be experiencing issues with the orphan, conditional, or special Marketing Authorization requests, might summarize the dossier. In the case of pediatrics, verify that the pediatric plan is in compliance 60 days before the admittance. In the United Kingdom, the Paediatric Investigation Plan (PIP) contains information on the procedures for looking into drug use in children, including compliance check information. The MHRA will set the deadline for CHM filings.

3. Decentralised and Mutual Recognition Reliance Procedure:

Under the EU's decentralized and mutual recognition procedure, the MHRA may rely on approval from any EU or EEA member state for marketing authorizations under the new Decentralized and Mutual Recognition Reliance Procedure for Marketing Authorizations (MRDCRP), which applies to both the UK and Great Britain. The MHRA stipulates that the first evaluation cycle needs to be finished by day 42. The marketing authorization is approved in the event that there are no issues. If there are any RFIs, the application processing time may be extended by 28 days. The MHRA has the right to object on Day 65, ask for significant modifications to the product information, or voice concerns about the extension of the federal procedural term for appeals.

Evaluation reports that are missing or incomplete dossiers may cause delays. The MHRA issues marketing authorizations by Day 67 if there are no objections by Day 65. An applicant's PL or PLGB number is required. The information must be sent to MHRA by the applicant via an eCTD. The applicant must demonstrate that the entire dossier, which is required to be accessible in the accessed dossier, is authorized under mutual recognition or a decentralized method in accordance with the EU, Reference Member States (RMS), and Concerned Member States (CMS). All assessment results, end-of-procedure papers, and projected © International Journal of Novel Research and Development (www.ijnrd.org) b671 product information can be given, subject to the initial EU application and any further changes.

Applicants seeking orphan status must submit a Great Britain (GB) form. When pediatric rules in the UK or the EU are in force, the eCTD needs to include an overall table and accompanying data. The cover letter sent by the applicants should provide a summary of the assessment, a decentralized approach or common standard numbers, product information variations, and paediatric requirements. Furthermore, the accompanying letter needs to confirm that the MRDCRP application is the same as approval from an EU or EEA member state.

4. European Commission (EC) Decision Reliance Procedure:

The Medicines and Healthcare Products Regulatory Agency (MHRA) in the UK is now able to rely on approvals that fall under the European Union's centralized system thanks to the European Commission's (EC) Decision Reliance mechanism. The European Union Commission Decision Reliance Procedure (ECDRP) will be available for business every two years. The UK Marketing Authorizations yielding under the ECDRP will soon be evaluated by the MHRA. Nevertheless, a delay in filing will affect the 67-day deadline. In the event that the MHRA makes significant objections or requests changes to the outcome, the application may be delayed.

The MHRA disputes that incomplete or erroneous dossiers might be the reason for these delays. The submission of the form five days after the CHMP opinion may cause a delay in the UK clearance process. By Day 46, MHRA guarantees to address concerns about early capitulation in order to address evaluation-related issues without causing the 67-day plan to be delayed. A Great Britain Product License (PLGB), also known as a Great Britain Marketing Authorization number, is required. The applicants should submit a letter of intent following the expectation of a positive CHMP assessment.

The letter of intent includes:

- The applicant's statement indicates that he or she will apply for the ECDRP.
- Publication of all CHMP evaluation reports.

After receiving EU permission, the UK authorization application can be filed whenever you'd like, though the organization encourages applicants to submit it as soon as the CHMP renders a favourable verdict. You can send the eCTD to MHRA Submissions along with the CHMP answers. The applications for centralized processes need to include the results of the CHMP evaluation review and the proposed products. The paperwork is required in order to receive orphan status. The eCTD needs to provide an overview table and paedology guidelines. The cover letter supplied by the applicants should include the number of the centralized procedure and evaluation reports, a list of the pediatric requirements, and other statements on how the Commission and CHMP approve the ECDRP application. Additionally, the applicant must vouch for the following:

- Delivering the letter of decision, the same day it is accepted.
- A commitment made by the EU Committee on Orphan Drugs.

NI (NORTHERN IRELAND) MARKETING AUTHORIZATION PROCEDURE/ UNFRETTED ACCESS PROCEDURE (UAP):

Great Britain can now approve medications while retaining the use of the present Northern Ireland marketing authorization by following the guidelines of the Unrestricted Access Procedure for Northern Ireland Marketing Authorizations. The MHRA makes a decision on recognition appeals within 67 days of validation. Many British marketing authorizations will be accepted by the forty-second day. The MHRA states that the errors must be fixed in 67 days. Erroneous or absent dossiers may cause delays. The requirements for qualification are outlined in this marketing authorization procedure, which also offers guidance on how to apply for a marketing authorization in Great Britain through the Unfretted Access Procedure (UAP).

The EU (Withdrawal) Act 2018's Section 8C (6) governs access to the UAP, and the UK was given the authority to control whether the holder of an essential marketing authorization was headquartered in Northern Ireland or not. For the applicant to submit the dossier, a current PLGB number is required. All answers to questions, the marketing authorization letter, final reviews, all supporting material (including product details for the initial UK or EU application) and any revisions must be provided by the applicant. In order to request status for a rare medicine, applicants must attach a GB form to their eCTD.

III. YELLOW CARD:

Pharmacovigilance (PV) programs have seen an increase in the significance of patients reporting unexpected sudden adverse drug reactions (ADRs) in recent years. The importance of patient feedback in pharmacovigilance was organized under EU law in 2012. By expressing symptoms, patients and medical professionals can communicate more effectively in both directions and gather information on the intensity of adverse reactions and their effects on quality of life. Patients in the UK can report possible adverse events to the MHRA by phone, mail, or online through the Yellow Card initiative. Every Yellow Card report was evaluated in previous studies on the identification of new drugs.

CONCLUSION:

The UK's regulations pertaining to pharmaceuticals and medical devices have changed somewhat as a result of Brexit. Since then, the Medical and Healthcare Products Regulatory Agency (MHRA) was founded in the UK as its own administrative organization. Brexit had a significant impact on international collaboration, EU politics, and the economy. A lot of representative states were prompted to vote under Article 50. According to Article 50, any member state may decide to quit the European Union after consulting with others. The associate state must notify the European Council of its intention to withdraw if it decides to do so. Following Brexit, the UK implemented a number of marketing authorization processes, including open access, continuous rolling evaluations, and 150-day nationwide assessments. The General Product Safety Regulations 2005, as per MDR 2002, outline the necessary standards for every medical equipment. Before putting their products on the market, medical device manufacturers have the option to brand their products with either the CE or UKCA labels. The UK Ministry determines that compliance with MDD legally requires adherence to ISO 13485, Medical Devices-Quality Management System. The Yellow Card Program was introduced by the Medical and Healthcare Products Regulatory Agency with the aim of improving adverse medication occurrences.

REFERENCES:

[1] "POST-BREXIT REGULATIONS OF DRUG PRODUCTS AND MEDICAL DEVICES IN THE UNITED KINGDOM", International Journal of Novel Research and Development (www.ijnrd.org), ISSN:2456-4184, Vol.8, Issue 7, page no.b668-b672, July-2023, Available :http://www.ijnrd.org/papers/IJNRD2307174.pdf

[2] Medicines and Healthcare Products Regulatory Agency. New guidance and information for industry from the MHRA – GOV.UK. Last updated 27 March 2023. (Accessed on 10 April 2023). https://www.gov.uk/government/collections/new-guidance-and-information-forindustry-from-the-mhra.

[3] Criado B, Bancsi M. The UK regulatory landscape post Brexit. Regulatory Focus. May 2021. Regulatory Affairs Professionals Society.

[4] Medicines and Healthcare Products Regulatory Agency. Regulations of Drugs and Medical Devices. MHRA – GOV.UK. (Accessed on 9 April 2023)

https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency

[5] Claire Dyer, Daniel Smith. A Guide to the UK Regulation of Medicines and Medical Devices Post-Brexit. Cetara. January 2023.

[6] Schengen Agreement. (Accessed on 11 April 2023)

https://www.schengenvisainfo.com/schengen-agreement/

[7] Medicines and Healthcare Products Regulatory Agency. Register Medical Devices to Place on the Market. MHRA – GOV.UK. December 2020.. https://www.gov.uk/guidance/register-medical-devices-to-place-on-the-market

[8] Medicines and Healthcare Products Regulatory Agency. Handling of Active Substance Master Files and Certificate of suitability. December 2020 MHRA – GOV.UK. https://www.gov.uk/guidance/handling-of-active-substance-master-files-and-certificates-of-suitability--2

[9] Medicines and Healthcare Products Regulatory Agency. Product information about medicines. December 2019. MHRA – GOV.UK. https://www.gov.uk/guidance/find-product-information-about-medicines

[10] MHRA. Medicines: register to manufacture, import or distribute active substances. December 2014.MHRA – GOV.UK.

https://www.gov.uk/guidance/medicines-register-to-manufacture-import-or-distributor-activesubstances#:~:text=on%20MHRA%2D%20GMDP%20.-,The%20registration%20process,it%20will%20take%2090%20days.

[11] KAMARAJ R, & PANGA YAMINI. (2022). Current Pharmaceutical Regulations of United Kingdom: POST BREXIT. Journal of Pharmaceutical Negative Results, 3406–3415. https://doi.org/10.47750/pnr.2022.13.S06.455

[12] Exiting the European Union consumer protection https://www.legislation.gov.uk/ukdsi/2019/9780111179260/pdfs/ukdsi_9780111179260_en.pdf

[13] Make an application for a licence to sell medicines in the UK. MHRA – GOV.UK https://www.gov.uk/guidance/apply-for-a-licence-tomarket-a-medicine-in-the-uk#application-\sprocess.

[14] Variations to Marketing Authorisation (MAs). December 2020. MHRA – GOV.UK https://www.gov.uk/guidance/variations-tomarketing-authorisations-mas

[15] Unfettered access procedure for Marketing Authorization approved in Ireland .uk/guidance/unfettered-access-procedurefor-marketing-authorisations-approved-in-northern-ireland

[16] Marketing authorisations, variations and licensing guidance. Medicines, Medical Devices and blood regulation and Safety https://www.gov.uk/topic/medicines-medical-devices-blood/marketing-authorisations-variations-licensing

[17] Yellow cards Make medicines and medical devices safer. MHRA – GOV.UK https://yellowcard.mhra.gov.uk/

[18] Patient safety https://www.who.int/news-room/fact-sheets/detail/patient-safety

[19] Medicines and Healthcare Products Regulatory Agency (MHRA)/Yellow Card: Report a problem with a medicine or medical device. MHRA – GOV.UK https://www.gov.uk/report-problem-medicine-medical-device

[20] Medicines and Healthcare Products Regulatory Agency. Consolidated version of the treaty on European Union. MHRA – GOV.UK https://www.legislation.gov.uk/eut/teu/article/50