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POST-BREXIT REGULATIONS OF DRUG PRODUCTS AND MEDICAL DEVICES IN THE UNITED KINGDOM

[1]P. Shailaja, [2]S. Jhansi, [3]T. Susmitha, [4]G. Snehalatha

[1]Associate Professor, [2, 3] Student,[4] Research Scholar
[1]Department of Pharmaceutical Regulatory Affairs,
[1]A.U. College of Pharmaceutical Sciences,
Andhra University, Visakhapatnam, India

Abstract: The Medical and Healthcare Products Regulatory Agency (MHRA) is the regulatory body in the United Kingdom. The MHRA is the in-charge for regulation of pharmaceuticals and medical devices in the UK. The term Brexit refers to United Kingdom's exit from European Union. Before Brexit, the guidelines for marketing medical devices and pharmaceuticals were under the European Medicines Agency (EMA) jurisdiction. On January 31, 2020, the United Kingdom formally exited the European Union. Thus, the Medical and Healthcare Products Regulatory Agency was created. The United Kingdom comprises four nations namely Scotland, Wales, England and Northern Ireland. The licencing for drug marketing was done in the portal of the Medical and Healthcare Products Regulatory Agency website. The documents are submitted in electronic Common Technical Document format by the applicant through the MHRA portal. There are various new marketing authorization assessment routes announced by MHRA for the marketing of drugs and medical devices. The Yellow Card scheme was developed in the UK for collecting adverse effects data of medicinal products directly from patients online on the website of the Medical and Healthcare Regulatory Products Agency which aids in medication research and new drug investigation.

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

I. INTRODUCTION

The European Union (EU) is a confederation of 28 nations. It was initially built on the rubble of World War II to end decades of warfare and develop fiscal cooperation between the states. The UK joined as one of the member states of the European Economic Community (EEC) established in 1973 and later it was changed into the European Union (EU), established in 1993 to enhance fiscal cooperation. The UK has never been close to the EU since the beginning. It has its own currency, the pound sterling and did not participate in the Schengen agreement. The Schengen Agreement is a treaty signed on June 14, 1985, by the European Union covering the gradual abolishment of the internal borders between the five European member countries namely Belgium, Germany, Luxemburg, France and the Netherlands in Schengen, a small village in Southern Luxemburg on the river Moselle. There have always been opponents of this Schengen concept in the British political scene and their number increased following the 2008 financial crisis. In 2012, when David Cameron was the prime minister, he promised to hold an election on whether the UK should remain a member of the EU. He stuck to his word and the UK held the referendum on June 23, 2016, but he resigned before the results were announced. Later, the proposal for Brexit first happened on March 29, 2019, and it really took place on January 31, 2020. After Brexit, the United Kingdom established its own regulatory authority, the Medical and Healthcare Products Regulatory Agency (MHRA). There were certain changes took place in the administrative aspects and laws of the United Kingdom after the exit from European Union. The UK made several changes in its regulations that differ from EU regulations.

APPLICATION OF LICENCE

The Applicants who want to market a new drug or medical device must log in to the MHRA portal for filing a marketing application. Everyone must submit the cover letter, and eAF (electronic application form) in e-CTD format. Application submissions without a cover letter and supporting materials could not be considered. For Pre-submission Checklist, the application submitted in Non-eCTD (NeeS) and eCTD is validated. When filing an application in the MHRA portal, the applicant must obtain a Product license (PL) number. The parts of the Pre-submission checklist for the application form consisting of:

Section 1: Type of Application

Section 2: Marketing Authorisation Application Particulars

Section 3: Other Marketing Authorisation Applications

Section 4: Annexed Documents

ACTIVE SUBSTANCE MASTER FILE (ASMF)

The Active Substance Master File (ASMF) was formerly known as European Drug Master File (EDMF). After Brexit, the EDMF was changed into UK ASMF. The purpose of this ASMF is to protect the manufacturer's valuable confidential intellectual property and assist the Market Authorisation holders in compiling a dossier for a Marketing Authorisation Application (MAA) or a Marketing Authorisation Variation (MAV) of a Medicinal product. The MHRA mandates Active Substance Master File from each applicant. The marketing authorization application must include the active substance master file (ASMF). In the UK, the Committee for Medicinal Products for Human Use (CMPU) which was formerly CHMP in the EU recommends the dossier be filed in an active substance master file. If any modifications are made to the dossier by the applicant, new and updated ASMF must be submitted using the MHRA submissions portal. By using the Active Substance Master File, the Marketing Authorisation holder is needed to transmit both the Applicant part (AP) and the Restricted part (RP). It consists of the following:

- 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 is a formatted summary of characteristics for instance the title of the drug, quantitative and qualitative makeup, pharmaceutical form along with analytic data, specifications, therapeutic characteristics, pharmaceutical data, Marketing Authorization Holder name, Marketing Authorization Number, the first authorization date or resumption date, the text's revision assignation are listed in the order must be submitted to the MHRA portal in the correct format using the SPC template. If the MA holder doesn't use this template for submission, the application will be denied. The applicant must simply needs to add the correct date to the template before sending it to the Medicines and Healthcare Regulatory Agency.

LICENSING REQUIREMENTS FOR DRUGS IN THE UK

Application process: All the UK and Great Britain (England, Scotland and Wales) national applications for drug approvals must put forward through the MHRA consent portal.

Format: eCTD

PL number: The applicant must get a Product License number from the MHRA portal prior to proposing the application.

Active Substance Master File: It is the MA holder's responsibility to make sure that the dossier is filed in ASMF only.

Summary of Product Characteristics (SmPC): The SPC template should not be altered in any way more than inserting the applicable information.

Enabling a name for the medicine to be marketed: Each request for a product name is considered carefully by the MHRA to ensure that the proposed name must allow the medication to be safe.

Fast-tracking the Market Authorisation: Applications may be subjected to fast-tracking if there is supporting evidence of benefit in an emergency involving public health or if there is a documented shortage of critical medication (DHSC).

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

Registration time: 60-90 days

LICENSING REQUIREMENTS FOR MEDICAL DEVICES IN THE UK

Application process: All the UK and Great Britain (Scotland, England and Wales) national applications for medical devices, IVDs and custom-made devices for registering in the market must be submitted through the MHRA submission portal. The applicant must register the medical devices on the MHRA DORS (Device Online Registration System).

Registration of Medical Devices: According to UK MDR 2002, the applicant must inform the MHRA prior to placing the device on the market.

Information needed while registering the devices

Manufacturer details:

- The manufacturer's name and address
- Company name as it appears on the device label/pack
- Trader Administrative Contact details
- A letter of designation

- A hand-written contract confirming UK person is responsible for mandatory responsibilities.

Device details:

- The Class of device namely Class I, Class IIa, IIb or Class III
- The Global Medical Device Nomenclature (GMDN) code
- Basic Unique Device Identification (UDI)
- Name of the Medical device (Brand name, trade or proprietary name)
- Model/version details
- Catalogue/Reference number
- Parameters like sterility contain latex, MRI compatible
- A copy of the Conformity Assessment certificate (United Kingdom Conformity Assessment (UKCA), CE (Conformite Europeenne), CE UKNI (United Kingdom Northern Ireland CE marking) if applicable

Fee: Each registration application for a medical device is subject to a jural charge of 100–240-pound sterling.

Registration time: 12-18 months

Plant Inspection: Mandatory

II. MARKETING AUTHORIZATION PROCEDURES FOR DRUGS IN THE UK

1. 150-day National Procedure
2. Rolling reviews
3. Decentralized and mutually recognised reliance procedure
4. The European Commission Decision reliance procedure and unrestricted access.

1. National Procedure/ 150 days procedure:

The National procedure is the most rapid marketing authorization procedure. The applications from the UK, Great Britain and Northern Ireland are examined by the MHRA within 150 days. During the 150-day procedure, there is a 60-day gap and the first evaluation is done within 80 days. Resolving First-phase issues (RFI letter) will be processed by "Info request" issued by the applicant. There are some exclusions to the 60-day rule. Orphan drugs are identified first. Round two begins after the candidate's response. To streamline CHM interactions, the MHRA will specify a "submission date" by interacting with Commission on Human Medicines (CHM). Before the deadline, the applicants need to contact the assessment team to coordinate with the schedule. The Applicants must send an email to the MHRA portal specifying the application's filing date and whether it pertains to the UK, Great Britain or Northern Ireland. A product description, CTD modules 2-5, the UK-specific CTD module 1 and an active substance master file are to be submitted. The cover letter is mandatory as it specifies whether the orphan status or merchandise approval is required.

2. Rolling review:

The Marketing Authorization is accelerated through rolling review/rolling assessment for the appeals involving a "complete dossier" of biological products or biosimilars. The eCTD dossiers of applicants are pre-assessed by MHRA. The risk of final-phase failure is reduced through modularity. The first module evaluation starts immediately and is followed up to sixty days. Following the assessment cycle, a Module Assessment Summary (MAS) is provided. By utilizing the Module Assessment Summary, the applicant can change the Module assessment summary (MAS). The last stage ought to take 2 months. The MHRA issues a Request for Information (RFI) on day 60 and the candidates have 30 days to provide a reply. The cycle starts again on Day 61 with final approval on Day 100. The applicant should request a pre-submission meeting to interpret the product characteristics, its target market and modules. Marketing authorization may be requested by the applicants within the UK, Great Britain, or Northern Ireland. The Quality data, non-clinical and clinical data may be presented separately or simultaneously under the modular method depending on the circumstances or the availability of the assessment team. The applicants in the final round consult the MHRA 90 days prior to final capitulation. The dossier can be summarised by the applicant at this phase who may have problems with the orphan, conditional or special Marketing Authorization requests. Regarding the case of paediatrics, check the conformity of the paediatrics plan 60 days preceding the accession. In the UK, the procedures considering the investigation of drugs in children including the compliance check information are provided in the Paediatric Investigation Plan (PIP). The CHM filing deadline will be determined by the MHRA.

3. Decentralised and Mutual Recognition Reliance Procedure:

The Decentralized and Mutual Recognition Reliance Procedure for Marketing Authorizations (MRDCRP) is a new marketing authorization procedure for the UK along with Great Britain from which the MHRA may rely upon approval from any EU or EEA member state under EU decentralised and mutual recognition procedure. The first round of evaluation, according to the MHRA must be completed by day 42. In the absence of any problem, the Marketing authorization is granted. The processing of applications may be delayed by 28 days if there are any RFI's. On Day 65, the MHRA may object, request remarkable changes to the product information or express concerns all over prolonging the appeals federal procedural period. Delays could be brought on by incomplete dossiers or missing evaluation reports. If there are no objections by Day 65, the MHRA grants marketing authorizations by 67 days. The Applicant needs a PL or PLGB number. The Applicant must provide the information via an eCTD to MHRA. The Applicant should portray that the whole dossier authorised under mutual recognition or decentralised procedure according to EU, Reference Member States (RMS) and Concerned Member States (CMS) be compelled in the accessed dossier. Contingent upon the initial EU application and any other updates, all evaluation results, end-of-procedure papers and anticipated

product information can be provided. A Great Britain (GB) form must be submitted by applicants to request orphan status. When EU or UK paediatric laws are in effect, the eCTD must contain supporting information and an overall table. The Applicants ought to submit a cover letter that includes a decentralised method or common standard numbers, product information variations, evaluation description and paediatrics requirements. Additionally, it must be affirmed in the cover letter that the MRDCRP application is equivalent to permission received from an EEA or EU member state.

4. European Commission (EC) Decision Reliance Procedure:

The European Commission (EC) Decision Reliance procedure outlines a new marketing authorization process for the UK that allows the Medicines and Healthcare Products Regulatory Agency (MHRA) to depend on approvals which are under the European Union's centralised procedure. Every two years, the European Union Commission Decision Reliance Procedure (ECDRP) will be opened. The MHRA will soon assess the UK Marketing Authorizations yielding under the ECDRP. However, a hold up in filing consequences the 67-day deadline. The application could be delayed if the MHRA issues notable complaints or demands output modifications. The MHRA disagrees such delays could be caused by missing or invalid dossiers. When the form is submitted five days subsequently the CHMP opinion then the UK approval possibly gets delayed. Early acquiescence concerns are guaranteed by MHRA by Day 46 to resolve evaluation-related problems without delaying the 67-day schedule. It is necessary to have a Great Britain Marketing Authorization number known as Great Britain Product License (PLGB). A letter of intent should be submitted by the applicants after a favourable CHMP assessment is anticipated. The letter of intent includes:

- Thirty days must pass between the proposal of the letter of intent and the form submission.
- The applicant's statement indicates that he or she will apply for the ECDRP.
- Publication of all CHMP evaluation reports.
- A statement stating if the petitioner wishes to apply for rare drug level.

The UK authorization application can be submitted at any time following EU approval; however, the organisation advises applicants to do so as soon as a favourable CHMP decision has been made. The eCTD with CHMP responses may be sent to MHRA Submissions. The applications for centralised processes must follow up facts on proposed products and CHMP evaluation review. The documentation is mandatory for orphan status. Paedology guidelines and an overview table must be provided in the eCTD. The number mentioned on the centralised procedure and evaluation reports, a list of the paediatric requirements and many statements regarding how the Commission and CHMP accept the ECDRP application must all be incorporated within the cover letter sent by the applicants. The candidate must also attest to 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)

The Unrestricted Access Procedure for Northern Ireland Marketing Authorizations outlines a new method for applying marketing authorization that enables Great Britain to approve drugs while still utilising the current marketing authorization for Northern Ireland. Within 67 days of validation, the MHRA decide the appeals for recognition. By the 42nd day, many British marketing authorizations will be accepted. According to the MHRA, the mistakes should be resolved within 67 days. Missing or invalid dossiers could result in delays. This marketing authorisation procedure lists the prerequisites for qualification and provides instructions on how to apply for a Great Britain marketing authorization under the UAP (Unfretted access procedure). The UAP can be accessed in accordance are bound to Section 8C (6) of the EU (Withdrawal) Act 2018 and the UK was authorised to regulate whether the essential Marketing authorization holder was headquartered in Northern Ireland. The applicant needs a valid PLGB number to submit the dossier. The applicant's information must furnish all responses to inquiries, the letter granting marketing authorization, final reviews, complete documentation including product details for the commencing UK or EU application as well as any amendments. A GB form must be attached to the eCTD by the applicants to request rare drug status. In the case of EU or UK paediatric laws, the documentation and an overview table must be included in the eCTD. The applicants must also include multiple affirmations that the UAP application complies with the NI approval, a process number, a list of finalized reports and a list of the essential paediatric amendments.

III. YELLOW CARD

In recent years, the importance of patients addressing unknown sudden adverse drug reactions (ADRs) has grown for pharmacovigilance (PV) programs. Under EU regulation in 2012, the significance of patient feedback in pharmacovigilance was organized. Expressing symptoms can help improve two-way communication between patients and healthcare professionals and collect data based on the severity and impact of adverse reactions on quality of life. Using the Yellow Card initiative in the UK, patients can notify the MHRA of potential adverse events online, by mail, or over the phone. Each Yellow Card report was assessed in earlier research on the discovery of novel medications. When citizens of the UK think there may be a problem with a drug or piece of medical equipment, they can report it as an "adverse event" through the Yellow Card Scheme. The MHRA may consult the manufacturer, a health care professional or both during an investigation. The UK regulatory authority uses the patient's Yellow Card Report in several ways:

- Marking the yellow card report on the UK portal database as a key safety issue and documenting similar problems to keep a record for surveillance of the product's safety.
- Making a note of the issue or effect from the patient's view to comprehend its implications.

CONCLUSION

Brexit has altered the regulatory aspects of drugs and medical devices in the UK to some extent. On January 31, 2020, the United Kingdom came out of the European Union. Since then, the UK established its own administrative body namely the Medical and Healthcare Products Regulatory Agency (MHRA). Brexit marked a huge impact on EU politics, economy and cooperation among other nations. Article 50 provoked many representative states to put vote. Article 50 states that any member state may choose to leave the European Union in conferring with their opinion. If the associate state determines to draw out, it ought to apprise the European Council of its objective. After Brexit, the UK adopted various marketing authorisation procedures like Nationwide assessments lasting 150 days, ongoing rolling reviews and open access. According to MDR 2002, the General Product Safety Regulations 2005 specify the required criteria for all medical devices. The manufacturers of medical devices can go for either UKCA marking or CE labels on the medical devices before they place for sale. The UK Ministry finds ISO 13485, Medical Devices-Quality Management System as a legal requirement to adhere to MDD. The Medical and Healthcare Products Regulatory Agency initiated the use of the yellow card program to evolve the adverse drug events.

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