Original Article

CURRENT PHARMACEUTICAL REGULATIONS OF UNITED KINGDOM: POST BREXIT

KAMARAJ R[1*], PANGA YAMINI[2]

[1,2]Department of Pharmaceutical Regulatory Affairs, SRM College of Pharmacy, SRM Institute of Science and Technology, Kattankulathur, Chengalpattu Dt., - 603203, India

Email: kamarajr@srmist.edu.in

DOI: 10.47750/pnr.2022.13.S06.455

Abstract

The Medical and Healthcare Regulatory Agency is a Healthcare agency which was established in the United Kingdom and regulates drugs and medical equipment. The guidelines for marketing drugs and medical equipment are under European Medicines Agency. The United Kingdom officially left the European Union on 31st January 2020. So, the Medical and Healthcare Regulatory Agency was started and the guidelines are given by them. The yellow card scheme was established and it collects the adverse effects data of medicals from the patients directly online on the Medical and Healthcare Regulatory Agency website which helps in drug development and new drug investigation. The licence for drug marketing was done through the Medical and Healthcare Regulatory Agency website. By submitting the documents in electronic Common Technical Document format. It will take around 12-18 months. There are some new marketing authorisation assessment routes Medical and Healthcare Regulatory Agency has published.

Keywords: Medical and Healthcare Regulatory Agency, United Kingdom, Yellow Card, Active Substance Master File, European Commission.

INTRODUCTION

On April 1, 2003, the Medical and Healthcare Regulatory Agency (MHRA) was founded in the UK to oversee pharmaceuticals and medical equipment. European Medicines Agency regulates medication and medical device marketing. On 31 January 2020, the United Kingdom leaves the European Union. The Medical and Healthcare Regulatory Agency gives guidelines. The yellow card initiative gathers adverse effects data from patients online at the Medical and Healthcare Regulatory Agency, which assists with medication development and new drug study. Marketing licences were obtained on the MHRA website. By submitting the documents in electronic Common Technical Document format. It will take around 12-18 months. Medical and Healthcare Regulatory Agency issued new marketing authorisation assessment pathways.

MHRA began. After thalidomide, the UK controlled drugs and medical equipment. In the 1950s and 1960s, Thalidomide addressed morning sickness. Since then, laws have been passed to regulate medications and medical equipment, such as the Medicines Act of 1968, which formed the Committee on Medicines Safety (CSM). The Philippines' Medicine Safety Committee oversees drugs. Healthcare Regulatory Agencies evaluate doctors and hospitals for safety and legality. Others separate industries and need opt-in. Medicines Control Body and Medical Devices Agency merged in 2003. In the 1990s, the UK began regulating medical gadgets. The STB formerly regulated medical equipment quality and safety. The scientific and Technical Branch joined National Health Service Procurement Directorate in the 1980s, which later became Medical Devices Agency. MDA and MHRA merged in 2003[1]. Medicines Control Agency and Medical Devices Agency merged in 2003 to become MHRA. It regulates human pharmaceuticals and medical equipment. No one regulates cosmetics, food, medications, or veterinary treatments. Mission violators may be prosecuted. Two years in jail and an infinite fine are possible [2]. The agency has raised public awareness of medications and equipment. The agency has promoted public health by assuring pharmaceutical and equipment safety. MHRA regulation has increased manufacturers' and pharmaceutical companies' adherence to standards and rules [3].

The UK officially broke relations with the EU on January 31, 2020, becoming the third nation. The transitional period began on February 1, 2020, and ends on December 31, 2020 [4].

PROMOTING AND ADVERTISING MEDICINES AND MEDICAL DEVICES IN THE UK

 UK law and norms restrict drug advertising. Brexit-related modifications to the Human

Medicines Regulations 2012 (HMRs) haven't affected medical product marketing, and UK law is consistent with Directive 2001/83/EC. 2010 Bribery Act includes advertisements.

 Medicines and Healthcare goods Regulatory Agency oversees advertising and publishes the Blue Guide. Most UK pharmaceuticals self-regulate.

 The ABPI Code and PAGB Code ban pharmaceutical advertising. Illegal. Non-prescription medications are for the public, whereas prescription medicines are for "medical professionals." No unapproved drug advertising [5].

 Act 2021 and Medical Devices Regulations 2002 govern medical devices. These include little limitations on advertising medical equipment, except tagging. ASA regulates UK ads. CAP codes are maintained. CAP Codes, not HCP, regulate medical device advertising (health and care professions). There are no online distance selling regulations [5].

YELLOW CARD

In recent decades, patient reporting of adverse drug reactions (ADRs) has been vital to pharmacovigilance (PV) operations. In 2012, European Union (EU) legislation formalised the role of patient feedback in medication safety [6]. Disclosing symptoms can assist uncover and assessing novel drug safety signals, gathering data on the frequency, severity, and influence of adverse medication reactions on quality of life, and enhancing two-way dialogue between patients and medical providers [7,8].

Under Yellow Card, UK patients report suspected adverse drug reactions to the MHRA. Adverse medication responses can be reported by phone, mail, or online. Previous research examined every Yellow Card report [9].

Through the Yellow Card Scheme, residents of the United Kingdom are able to report what is known as "adverse occurrence" when they believe there may be an issue with a drug or medical equipment.

- A medical equipment damages or almost hurts someone due to unclear labelling, damage, or misuse.
- A broken machine stops a patient from getting treatment.
- A medical device gives the wrong diagnosis to a person.
- A medication does not carry out its intended functions.
- A pharmaceutical product is of low quality.
- Have reason to believe that a medication or medical equipment is a knockoff or a fake.
- A medicine cause side effect [10]

MHRA may investigate with the manufacturer, a medical professional, or both. Even if not explored, it will be documented for future reference. If needed, the reporter will be notified. [10].

Medicines and Healthcare Regulatory Agency uses your Yellow Card Report in many ways such as:

- Highlighting the report on the MHRA database as a potential safety issue and recording similar complaints to keep a close watch on the product's safety.
- Noting the effect or problem from the patient's perspective to better appreciate its impact.

- To help MHRA scientists and experts evaluate the safety risk, we need further information.
- Investigating comparable Yellow Card reports to find new safety signs.
- Asking the product maker for further information (Manufactures).
- Discussion with regulatory organisations and experts about a prospective negative effect, incident, or issue [11].

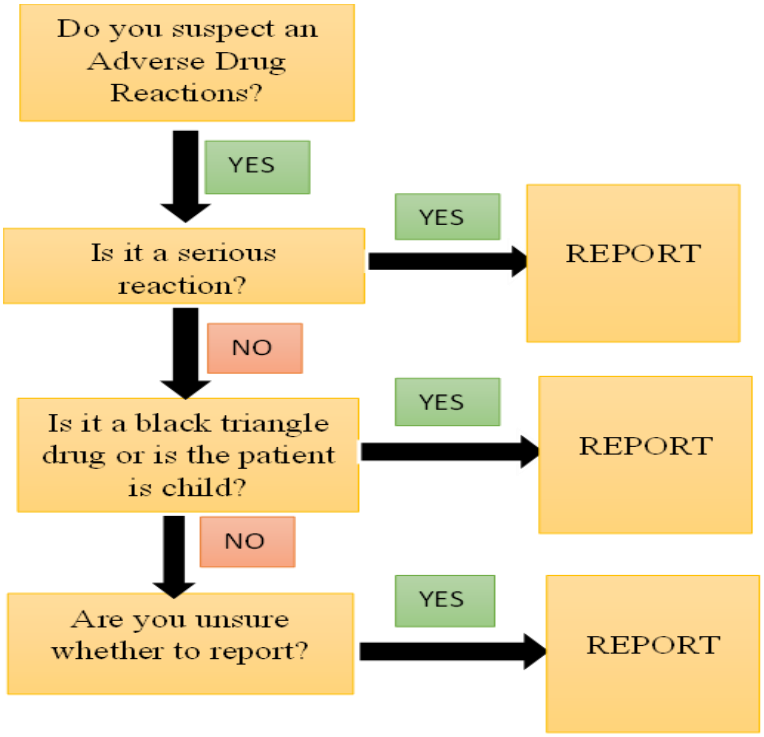

Figure 1. Reporting reminder flowchart helps to decide whether to report Adverse Drug Reactions

APPLYING FOR LICENCE

All applicants must use the MHRA website. Everyone must submit e-CTD (eCTD). Complete eAF and cover letter. The application may be invalid without a cover letter and documents. Pre-submission checklist Extedo Eurs validates NeeS and eCTD entries (EiY). Before applying for a UK licence, receive an MHRA PL number [12].

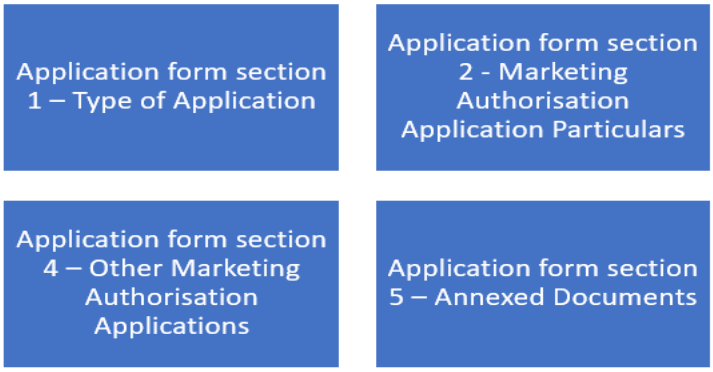

Figure 2. Pre- Submission Checklist Application Form Sections

Active substance master files (ASMFs)

MHRA needs substance master files. The Marketing Authorization application must include the Active Substance Master File (ASMF). Master file updates MHRA-submitted master file. CMPU recommends an active substance master file (CHMP). In the Marketing Authorization dossier, including the Applicant's Part (AP) of the Active substance master file and a file holder letter. When employing an Active substance master file technique, the file holder must send the AP and RP. This should include:

- A completed cover letter and administrative information form
- Any letter of access that is important
- The Quality General Executive Summary for both the AP and the RP
- The Expert's curriculum vitae

 MHRA wants an Active substance master file once. Essential paperwork should arrive one month before or after the MAA or MAV deadline. CMPU modifies Active substance master files.

 The owner of the Active substance master file must notify applicants/MA holders and the MHRA of any changes. Using the MHRA Submissions Portal, submit new and updated master files for active substances.

The UK no longer contributes to the EU's Active substance master file. UK national applications won't utilise the CTS ASMF review repository or EU/ASMF/XXXX reference codes after 1 January 2021.

Certificates of Suitability (CEPs)

Certificates of Suitability are made by the EDQM, so leaving the EU won't change anything about them (EDQM). Non-EU Council of Europe body. Directorate. The UK signed the European Pharmacopoeia Convention and is a Council of Europe member. The regulations for using Certificates of Suitability to support Marketing Authorization Applications have not changed.

Summary of product characteristics (SmPC)

The Medicines and Healthcare Regulatory Agency must receive the summary of characteristics in SPC format, which contain: (1) Name of the Medicinal Product, (2) Qualitative and Quantitative Composition, (3) Pharmaceutical Form, (4) Clinical Particulars, (5) Pharmacological Properties, (6) Pharmaceutical Particulars, (7) Marketing Authorisation Holder, (8) Marketing Authorisation Number, (9) Date of First Authorisation/Renewal of the Authorisation, (10) Date of Revision of the Text.

Everyone has to use this template if not their submission will get rejected. They just have to edit the template with the appropriate date without altering it [12].

Fast track your marketing authorisation

In a public health emergency or drug shortage, applications may be handled quickly (DHSC). We contacted RIS.NA@mhra.gov.uk for fast-tracking; 3 pages max. Email should include product justification, clinical features, and supporting data [12].

Rejection

Any submission not meeting MHRA standards excluded. If the submission is rejected, MHRA will send an email stating why, and we must resubmit the document with the problem corrected.

Table 1: Regulations and Licencing Requirements

Authority	Medical and Healthcare Product Regulatory Agency
Website for Registration	https://www.gov.uk/
Time Taken for Registration	12 – 18 months
Plant Inspections	Mandatory, if there's no PIC/S GMP Certificate available

Marketing Authorization of medical products and medical devices in the UK

A national marketing authorization application must be reviewed within 210 days, excluding procedural clock-stop. Post-Brexit, the MHRA has 150 days to review MA applications. Five-year MHRA approvals. Marketing authorizations expire after three years (the sunset clause). The Marketing Authorization is valid permanently after five years; safety concerns propose a five-year expiration [13].

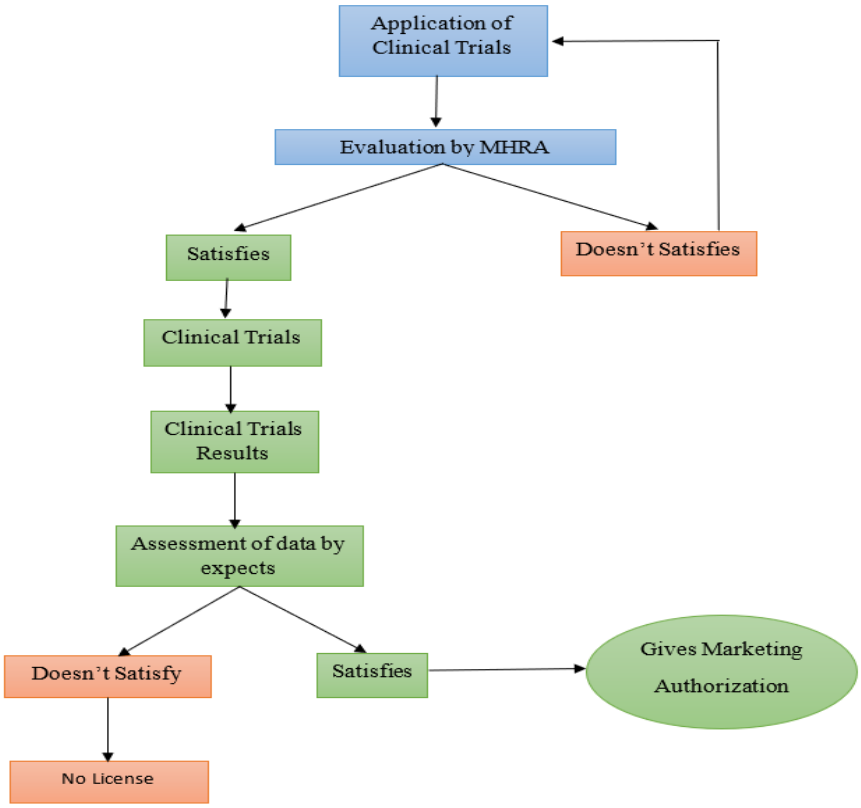

Figure 3. Marketing Authorization Process

MHRA GUIDANCE ON NEW MARKETING AUTHORIZATION ASSESSMENT ROUTES

The Medicines and Healthcare Products Regulatory Agency released information on new MA evaluation paths following Brexit: 150-day national assessments, the European Commission Decision reliance procedure, rolling reviews, decentralised and mutual recognition reliance care, and unhindered access.

150-Day National Assessments

The 150-day advice suggests a faster national MA assessment approach. The MHRA reviews UK, Great Britain, and Northern Ireland Marketing Authorization applications within 150 days. The guideline states that "any high-quality new Marketing Authorization applications submitted to MHRA" can use the application process and includes guidelines for novel active substances, biosimilar pharmaceuticals, and existing active substances. The guidance describes innovative active medications, biosimilars, and current active chemicals [14].

Timetable

The 150-day test includes a 60-day break. 80-day first assessment. "Info request" will resolve first-phase difficulties (RFI letter). Time-off should help. The 60-day clock-off rule has exceptions. First, orphans are identified. After the candidate's answer, round two starts. MHRA will designate a "submission date" to simplify CHM interactions (CHM). Before their response date, applicants should contact the MHRA Assessment Team to coordinate with CHM's meeting schedule.

Application process

The guidance explains what to do with new active substances and biosimilar products.:

- Actions to take prior to submission. Applicants should email AcceleratedandRollingReview@mhra.gov.uk with the submission date and whether the Marketing Authorization application is for the UK, GB only, or NI only.

- The purpose of the pre-application meeting, as well as any concerns the candidates may have and their desire to address them.

The guideline leads active substance applicants to MHRA's RMP guidance. Review UK-only MHRA bioequivalence recommendations. Advice for novel active medicines, biosimilars, and existing active substances. CTD modules 2-5, a UK-specific CTD module 1, a product description and patient education leaflet, and, if appropriate, an active ingredient master file. Cover letters are required. The cover letter should specify if orphan status or marketing approval is needed.

Appeals

Applicants can ask to have a decision not to give them a Marketing authorization A looked at again. Schedule 5 and paragraph 11 of Schedule 11 of the Human Medicines Regulations 2012 (SI 2012/1916) explain how to do a review.

Rolling Review

Rolling assessment for Marketing Authorization applications speeds up medication development. "Complete dossier" MA applications, including biological products, are eligible. Biosimilars count. MHRA pre-assesses applicants' eCTD dossiers. Modularity minimises final-phase failure risk.

Timetable

First module evaluation begins on Day 0 and lasts 60 days. A Module Assessment Summary (MAS) is given 60 days after each evaluation cycle. Modify modules using Module Assessment Summary (MAS). The last phase should take two months. By Day 60, the MHRA may issue an RFI; applicants have 30 days to respond. With approval on Day 100, the clock resumes on Day 61. The MA determines orphan status.

APPLICATION PROCESS

Pre-assessment of modules:

- Applicants should request a pre-submission meeting to discuss the product, its intended audience, and each submitted module. Applicants can get a Marketing Authorization for the UK, Great Britain, or Northern Ireland.

Depending on conditions and/or data availability, quality, non-clinical, and clinical data may be provided individually or concurrently under the modular method.

Final Phase:

Final-phase candidates create modules. 90 days before final submission, consult MHRA. Applicants may summarise the dossier and highlight any issues, such as orphan, conditional, or special Marketing Authorization requests. 60 days before submission, check paediatrics plan compliance. Compliance check information are in MHRA's Procedures for UK Paediatric Investigation Plans (PIPs). The MHRA will set a submission date for the CHM.

Appeals:

Applicants may seek a review of a non-approval utilising the method in Schedule 5 and paragraph 11 of Schedule 11 of the Human Medicines Regulations 2012. If an applicant appeals to the denial of orphan status, a Marketing Authorization won't be granted until the appeal is complete.

Fees:

The Medicines (Products for Human Use) (Fees) Regulations 2016 (SI 2016/190) say that there will be a fee for each phase of assessment (for the quality, non-clinical, and clinical modules).

EUROPEAN COMMISSION (EC) DECISION RELIANCE PROCEDURE

The European Commission (EC) Decision Reliance Procedure describes a new Marketing Authorization procedure for the UK that lets the MHRA rely on EC approvals under the EU's centralised procedure. From January 1, 2021, the European Commission Decision reliance procedure (ECDRP) will be open for two years.

Time Table:

The MHRA will review UK Marketing Authorizations under ECDRP as quickly as feasible, but a submission delay may effect the 67-day deadline. The MHRA may have major complaints or request significant product revisions, delaying the application. MHRA objects. Missing or incomplete dossiers might create delays. The application uses CHMP's opinion. 5 days after CHMP opinion, 67 days (provided the EC decision has been received). MHRA approval may be delayed if the application is lodged more than five days after the CHMP opinion. MHRA guarantees early approval issues. MHRA tries to fix evaluation issues by Day 46 without impacting the 67-day plan.

Application process:

The tutorial describes how to apply for a British Marketing Authorization under EC Decision reliance (ECDRP). Also, a dossier-receipt fee. A Great Britain Marketing Authorization (PLGB) number is required. Once a favourable CHMP opinion is expected, candidates should submit an intent letter which includes:

- Statement from applicant indicating he or she will apply for ECDRP.
- Four weeks must pass between the letter of intent and application submission.
- Disclosure of all versions of CHMP evaluation reports.
- A declaration indicating if the petitioner wants to seek orphan status.

A MHRA MA application can be submitted any time after EU approval, however the agency encourages applicants to submit immediately after a favourable CHMP decision. MHRA Submissions accepts a single eCTD with CHMP replies. If MHRA received the document without changes, it's unnecessary. Initial centralised process applications must contain CHMP evaluation

reports, comments, and proposed product information. GB paperwork needed for orphan status. eCTD must provide paediatric rules and an overview table.

Applicants must provide a cover letter containing guiding information, such as the centralised procedure number, a list of assessment reports, and paediatric requirements, and several statements about how the Commission and CHMP accept the ECDRP application. The applicant is also required to confirm:

- Delivering the decision letter on the day of receipt.

- Any EMA Committee on Orphan Medicinal Products ruling

DECENTRALISED AND MUTUAL RECOGNITION RELIANCE PROCEDURE

Decentralized and mutual recognition reliance process for marketing authorisations (MRDCRP) introduces a new Marketing Authorization procedure for the UK and Great Britain via which the MHRA may rely on approval from any EU or EEA member state under EU decentralised and mutual recognition processes.

Time Table:

- MHRA believes the first-round evaluation should be done by day 42. If no issues are found, Marketing authorization A is awarded. MHRA RFIs can delay application processing by 28 days. The MHRA commits to provide Marketing Authorizations within 67 days if no points remain by Day 65.

- The MHRA may raise objections, seek substantial modifications to product details, or raise concerns on Day 65, extending the application's national procedural time frame. Incomplete dossiers or missing evaluation reports may cause delays.

Application process:

A PL or PLGB number is necessary. Submit an eCTD via MHRA Submissions. The suggestion emphasises that the submitted dossier should be the entire dossier authorised under mutual recognition or decentralisation in the EU, including RMS and CMS issues. All RMS evaluation reports, end-of-procedure paperwork, and planned product details must be given for the first EU application and any revisions. To request orphan status, applicants must submit a GB form. The eCTD must include documentation and an overview table when EU or UK paediatric regulations apply.

Applications must include a cover letter with the guidance info. This contains common standards or decentralised procedure numbers, product info variances, evaluation reports, and paediatrics needs. The cover letter must additionally declare that the MRDCRP application is the same as the permission from an EU or EEA member state.

NORTHERN IRELAND APPROVES FLAWLESS ACCESS PROCEDURE FOR MARKETING AUTHORIZATIONS

Unfettered Access Method for NI Marketing Authorizations highlights a new Marketing Authorization application procedure that permits Great Britain approval of pharmaceuticals with the current Northern Ireland Marketing Authorization.

The MHRA will decide on recognition applications within 67 days after validation, however most British MAs should be accepted by the 42nd day. MHRA believes complaints should be handled within 67 days (after initial examination). The MHRA may object to product information, delaying application processing. Missing or incomplete dossiers might create delays.

Application Process:

The guidance sets out eligibility criteria and details of what applicants must do to apply for a Great Britain Marketing Authorization under the UAP.

The UAP is accessible if:

- The relevant Marketing authorization holder is established in NI.
- Section 8C (6) of the EU (Withdrawal) Act 2018 allowed the UK to regulate QNIG.

Required PLGB number. Unless an NI application is made, the dossier must be an eCTD through MHRA Submissions. Advice emphasises providing the entire authorised dossier, including solutions to concerns. The applicant must include evaluation reports, end-of-procedure documentation, the Marketing authorization grant letter, and product details for the original UK or EU application and any revisions.

Applicants must attach a GB form in the eCTD to request orphan status. When EU or UK paediatric requirements apply, the eCTD must contain documentation and an overview table.

Applications must contain a cover letter with the NI process number, a list of assessment reports, and paediatric requirements, and several declarations on the UAP application's compliance to the NI approval on which it is constructed [15].

IMPACT OF BREXIT ON THE UK

After Brexit, the UK's economy and politics were unpredictable, impacting the EU and globally. Key political factions must agree on the UK's leave date, negotiations, and Article 50. Several MPs have recommended holding general elections before withdrawing, which would require altering the Fixed-term Parliaments Act 2011. Gibraltar, Greater London, Scotland, and Northern Ireland chose to stay, whereas most of England and NI opted to leave, worrying Irish and Scottish nationalists. The Foreign Affairs Select Committee found in July that PM Cameron blocked Brexit preparations, calling it deplorable negligence. Brexit's economic effects have been contested since the referendum. Remainers and the UK Treasury agreed that EU membership was good for trade, but Leavers believed eliminating net payments would lower taxes and boost government expenditure. Spending boosts the economy [16].

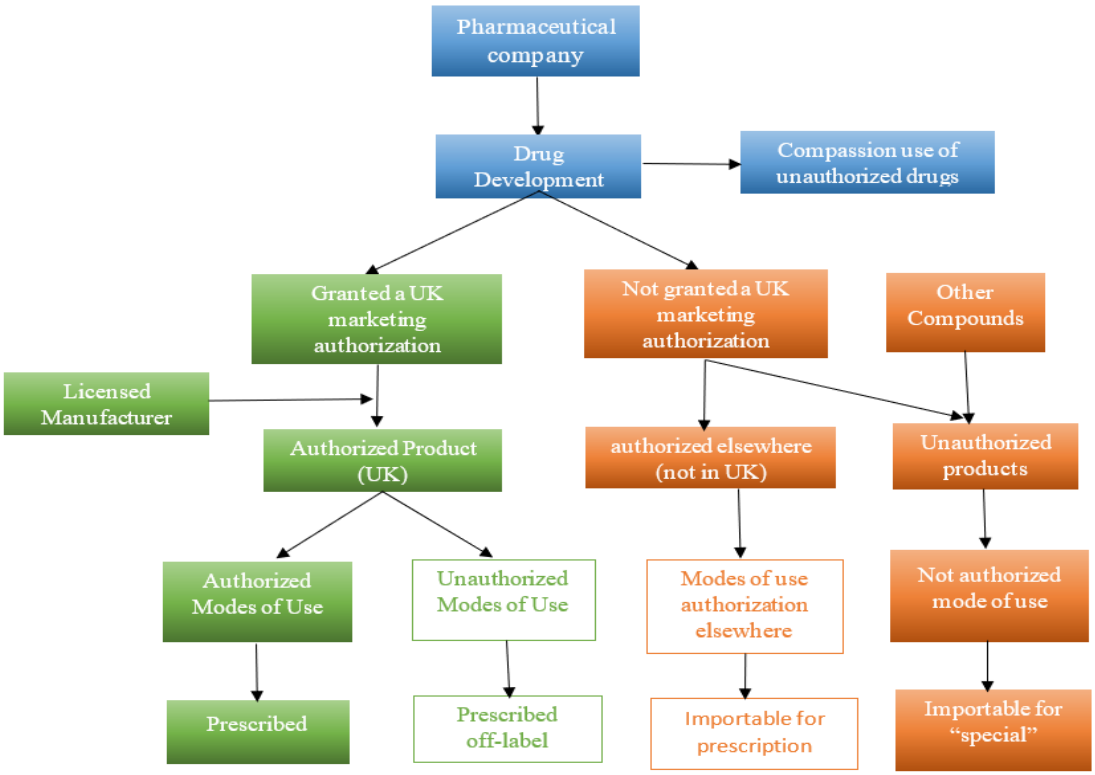

Figure 4. Marketing authorization in the UK

CONCLUSION

Brexit changed UK drug laws. MHRA oversees UK drugs (Medical and Health Regulatory Agency). MHRA utilised yellow cards to identify medication side effects. After Brexit, the Medicines and Healthcare Products Regulatory Agency will have 150-day nationwide assessments, rolling reviews, and unlimited access. Brexit impacted Britain's economy, politics, the EU, and the world. Article 50 needs approval. Early elections need modifying the 2011 Fixed-term Parliaments Act. Irish and Scottish nationalists were furious that Gibraltar, Greater London, Scotland, and Northern Ireland stayed. England, Wales, and unionist Northern Ireland left. Cameron banned Brexit planning in July, according to the FASC. Unknown are Brexit's economic implications. Lower net payments would reduce taxes and increase government spending, argued leavers. Treasury agrees EU membership helps trade. Consumption increases GDP.

REFERENCES

[1] StudyCorgi. (2022, April 2). Medicines and Healthcare Regulatory Agency (MHRA). Retrieved from https://studycorgi.com/medicines-and-healthcare-regulatory-agency-mhra/
[2] MHRA. (2008). Medicines and Medical Devices Regulation: What You Need to Know. MHRA.
[3] Treweek, G. L, Heller, T & MacQueen, H. (2006). Complementary and Alternative Medicine: Structures and Safeguards Book 2 of Perspectives on complementary and alternative medicine. Routledge.
[4]31 January 2020 EMA/40083/2020 Media and Public Relations/www.ema.europa.eu.
[5] Hazell, L., Cornelius, V., Hannaford, P., Shakir, S., Avery, A. J. How Do Patients Contribute to Signal Detection? Drug Safety, 36(3), 2013, 199–206.
[6] Van Hunsel F, Härmark L, Rolfes L. Fifteen years of patientreporting. what have we learned and where are we heading to Expert Opin Drug Saf. 18(6), 2019, 477-484.
[7] World Health organisation. Patient safety. 2019. https://www.who.int/news-room/fact-sheets/detail/patient-safety
[8] Avery AJ, Anderson C, Bond CM, et al. Evaluation of patient reportingof adverse drug reactions to the UK'Yellow Card Scheme': literaturereview, descriptive and qualitative analyses, and questionnairesurveys.Health Technol Assess. 15(20), 2011, 1-234,
[9] Medicines & Healthcare products Regulatory Agenc (MHRA) / Yellow Card: Report a problem with a medicine or medical device https://www.gov.uk/report-problem-medicine-medical-device.
[10] https://yellowcard.mhra.gov.uk/information
[11] Apply for a licence to market a medicine in the UK https://www.gov.uk/guidance/apply-for-a-licence-to-market-a-medicine-in-the-uk#application-process.
[12] Handling of Active Substance Master Files and Certificates of Suitability (https://www.gov.uk/guidance/handling-of-active-substance-master-files-and-certificates-ofsuitability--2).
[13]https://www.lexology.com/library/detail.aspx?g=9cedb84c-49ac-4b20-ba05-12cc5c7926ad (lexology, October 20 2021)
[14]Ankit, Trivedi, Shrikalp, et al. Transition of Pharmaceutical Regulations: The New Regulatory Era after Brexit. Journal of Pharmaceutical Research International 33(47A), 2021, 804-817.
[15] MHRA: New guidance and information for industry from the MHRA.
[16] Syed Haider Ali Zaidi, Xin-Yu Wang, Sardar Ahmed, et al. Brexit: A review of impact on future of United Kingdom outside the European Union. International Journal of Modern Research in Management, 1-1, 2017, 14-33.