Pharmaceuticals Export Promotion Council of India

(Set up by Ministry of Commerce & Industry, Government of India)

REGULATORY & MARKET PROFILE OF UNITED KINGDOM

DEMOGRAPHY

SL. No	Parameter	Description
1	Region	Western Europe
2	Country	UK
3	Capital	London
4	Population	65.648.100 (July 2017 est)
5	Population growth rate (%)	0.52%(2017est)
6	GDP (purchasing power parity)	**$** 2.88 trillion **(**2017est.)
7	GDP - real growth rate (%)	1.7 % (2017 est.)
8	GDP - per capita (PPP)	$ 43,600(2017 est.)
9	Epidemiology	Cancer, Cardiovascular diseases, chronic respiratory diseases, neurological disorders and diabetes, urogenital, blood and endocrine diseases Musculoskeletal disorders and Mental and behavioural disorders
10	Population below poverty line	15 %(2013 est)(No update)
11	Age structure (%)	0-14 years: 17.53%
		15-24 years: 11.9%
		25-54 years: 40.55%
		55-65 years : 11.98%
		65 & above: 18.04%
Source: CIA World Fact Book		

Introduction

The UK government is committed to health spending and the National Healthcare Service (NHS) and this outlook. Government will continue to contribute more to overall healthcare expenditure; however, a focus on cost containment will mean that government health expenditure as a percentage of total health expenditure will fall over the next decade. The decline in overall healthcare spending will ultimately have an impact on drug expenditure, in particular high value and high volume therapeutics.

An ageing population, a preference for innovative medicines and the population's access to new and advanced healthcare technologies will result in the continued growth of the UK's pharmaceutical market.

Pharma Expenditure

Medical expenditure was $ 44.63 billion in 2017 with a negative growth of 2%.

Strengths:

- The UK's pharmaceutical market is among the 10 largest in the world.
- The UK is the main base for GlaxoSmithKline and AstraZeneca, two of the world's major multinationals, as well as a key site for most other drug majors.
- The regulatory environment is one of the fairest and most transparent in the world.
- The government-industry relationship is mostly one of collaboration.
- Government's cost Cutting measures is encouraging increased usage of Generics.

Opportunities

- The OTC market growth is driven by government support for self-medication.
- Changes in the retail sector, such as increased pharmacy opening hours, primary care services in grocery stores and expanded pharmacy services and prescribing power for pharmacists, should help drive growth.

Market Overview

England constitutes 84% of the total Pharma expenditure, while the rest is spent in Scotland, Wales & Northern Ireland. The pharmaceutical market of UK is one of the largest in entre Europe and is a key market. By 2021 with a CAGR of 2.7% is likely to reach $ 52.01 bn. Uk was among the top ten markets in 2016 with percapita spending at $ 692.

Non-communicable diseases dominate the country's disease burden. In 2016, the type of diseases that posed the highest burden included cancer, cardiovascular diseases, musculoskeletal disorders and mental and behavioural disorders. Cardiovascular disease is the most frequent cause of death in the UK, followed by cancer, chronic respiratory diseases, neurological disorders and diabetes, urogenital, blood and endocrine diseases.

Biotechnology

The UK is the world's third largest global hub for innovation and development in the biosciences sector. According to the UK BioIndustry Association (BIA), the UK raised more venture capital than San Diego in 2016 and is primed to close the gap on San Francisco and Boston as the two leading centres for life sciences. The BIA's report found that the UK had the most robust clinical pipeline in Europe after

another impressive year in 2016, despite economic uncertainties surrounding the vote to leave the European Union. UK-based biotech firms raised a total of GBP1.13bn in 2016.

Brexit Evaluation

- Weak economy persists, limiting NHS funding and expenditure on medicines.
- Possibility of the NHS benefiting from extra funding as part of the EU budget dividend, providing extra resources to expand services and increase investment in new medicines
- Slower immigration reduces demand for healthcare services, with lower tax receipts from migrants diminishing funding streams for the NHS and medicines.
- Some of the 1.2mn Britons who have elected to live in the EU, including many pensioners, return to the UK increasing the demand for healthcare services and consumption of pharmaceuticals
- Staff shortages exacerbated due to restrictions on EU citizens working for the NHS and an exodus of staff seeking more attractive employment prospects abroad reduces access to healthcare and pharmaceuticals.
- UK status as innovation hub compromised due to reduced R&D funding and slower uptake of innovative medicines as a result of increased pricing pressures.
- Market becomes less attractive for multinationals due to a weak pound and uncertainties surrounding the Brexit process.
- Manufacturing investment increases as companies seek to take advantage of a more competitive (as it becomes weak) currency to expand exports, boosting economic growth and access to domestically produced medicines.
- The UK develops more progressive pharmaceutical regulations unencumbered by EU directives, making it an attractive market to launch products ahead of the EU.

Generic Market

The UK pharmaceutical market will continue to observe a relatively high level of generic penetration. Generic drug sales growth is expected to slightly outpace the patented medicine market over the next five years.

Generic drug market was at $ 12 billion in 2016. At a CAGR rate of 3.7% till 2021, the generic market is forecasted to touch $ 14.4 bn.

84% of the prescriptions generated are of generic drugs.

The policies implemented to increase generic usage is as follows.

- Generating and supporting a clinical culture that encourages generic prescribing.
- Technological support to make generic prescribing easier - for example, use of the Prescribing Rationally With Decision Support In General Practice Study (PRODIGY) software, which prompts GPs to prescribe generic alternatives - as well as peer comparison and advice through the collection and dissemination of detailed GP prescribing information and individual advice on prescribing.
- The use of financial incentives - such as those embodied in the GP fund holding scheme.

- Direct market intervention - such as the 'Category M' scheme introduced in 2005/6 to reduce the price of generic medicines.
- Regulation - such as the use of compulsory generic substitution.

Pharmaceutical Trade

Despite Brexit, UK will remain one of the major global exporters of pharmaceutical goods, with leading multinationals continuing to produce high-value pharmaceutical products.

In 2016 UK had a small negative trade balance. Exports of Pharma accounted for $ 31.23 billon and imports were $ 31.7 bn.

Pharma was one of the two-fastest-growing UK export categories to Bangladesh, Nigeria, Indonesia and Kenya over 2011-2015. Pharmaceuticals are already the second largest UK export category to Mexico and Vietnam.

UK's exports to EU countries were growing only by 29.2% touching $ 3.5 bn between 2005-2015, exports to non EU went up by a whopping 124% during the period to $ 11.4bn. The US leading the list of Non-EU export partners.

The leading export destinations for UK-made medicines include other developed markets, led by the US, Germany, Spain, France, the Netherlands and Italy. The leading countries of medicines imports into the UK are Belgium, Ireland, Germany, the US and Switzerland, reflecting the advanced nature of the market.

Local Industry

The UK has a strong pharmaceuticals industry that is a considerable force on the international market. The vast majority of major multinationals are also present through local subsidiaries engaged in marketing, manufacturing and R&D. The leading local companies in terms of market value and market capitalisation are GlaxoSmithKline and AstraZeneca. The UK also boasts a large number of smaller companies specialising in R&D and biotech products.

The Annual Business Inquiry report published by the Office for National Statistics (ONS) shows that the number of enterprises for manufacturing pharmaceuticals (basic pharmaceutical products and preparations) increased from 444 in 2010 to 528 in 2013, marking a 16% rise, according to data published in June 2015.

R&D

UK researchers have also been responsible for around a fifth of all discoveries and development of the world's top medicines. In fact, the industry accounts for 60% of R&D investment in the UK, according to Stephen Whitehead, the CEO of the Association of the British Pharmaceutical Industry (ABPI). As of 2015, the UK based pharmaceutical industry directly employs around 73,000 people (up from 72,000 employees in 2009), of which 32% work in R&D.

Statistics:

India's Exports of Pharmaceuticals to U K						
Category	**2015-16**	**2016-17**	**2017-18**	**GR%**	**Contbn%**	**Contbn to Region**
BULK DRUGS AND DRUG INTERMEDIATES	82.84	85.64	78.15	-8.75	14.04	8.67
DRUG FORMULATIONS AND BIOLOGICALS	458.59	438.69	454.29	3.56	81.60	28.13
AYUSH	1.23	1.32	1.55	17.18	0.28	6.94
Herbal Products	9.88	9.25	9.79	5.82	1.76	9.37
Surgicals	11.18	14.16	12.76	-9.92	2.29	12.27
Vaccines	0.04	0.75	0.16	-78.70	0.03	5.55
Total	563.76	549.81	556.70	1.25	100.00	20.24

UK was the second largest Exporting partner of India during 2016-17, only after USA. UK is also the second largest exporting partner of India's formulations and it is the 13th largest exporting partner of Bulk drugs.

Issues:

At present Issues encountered with EU are the issues applicable to UK.

1. **Delay in the exported consignments reaching the market.**

EU tests analytically each and every batch of Pharmaceutical products imported at the port itself. This delays the product's entry into the market sometimes even by 2-3 months.

2. **Cost of Meeting Technical requirements.**

Generic formulation dossiers may need to be frequently changed after the market authorization also. To get all such changes ratified, they have to be filed along with the prescribed fee. The fee levied in such cases becomes very high for a product with multiple countries' authorization. Besides, every post approval safety review (PASR) is to be ratified through a format called " 1b" showing the compliance of safety approval and the fee levied in such cases are very high and varies from country to country.

Change in address of the manufacturing site sometimes arising out of administrative procedures of the local government of the state/ city even though a physical shift is not involved (Example bifurcation of states, Reorganization of districts in a state) are also being considered on Par with a physical shift the site and the fee levied accordingly.

REGISTRATION AND LICENSING REQUIREMENTS

➢	Regulatory Authority	:	**Medicines & Healthcare products Regulatory Agency (MHRA)**
➢	Website of regulatory Authority	:	https://www.gov.uk/
➢	Fees for Drug Registration	:	GBP 24760-29000
➢	Normal time taken for registration	:	12 - 18 Months
➢	Registration Requirement [Dossier Format]	:	e-CTD
➢	Whether plant inspection is mandatory	:	Yes, if no PIC/S GMP certification available
➢	Requirement of Local agent/ Subsidiary		Subsidiary is Required to operate locally

MHRA Organization:

The Medicines and Healthcare products Regulatory Agency regulates medicines, medical devices and blood components for transfusion in the UK.

The agency has 3 centers:

- the Clinical Practice Research Datalink (CPRD), a data research service that aims to improve public health by using anonymized NHS clinical data
- the National Institute for Biological Standards and Control (NIBSC), a global leader in the standardization and control of biological medicines
- the Medicines and Healthcare products Regulatory Agency (MHRA), the UK's regulator of medicines, medical devices and blood components for transfusion, responsible for ensuring their safety, quality and effectiveness

The agency is responsible for:

- ensuring that medicines, medical devices and blood components for transfusion meet applicable standards of safety, quality and efficacy
- ensuring that the supply chain for medicines, medical devices and blood components is safe and secure
- promoting international standardisation and harmonisation to assure the effectiveness and safety of biological medicines
- helping to educate the public and healthcare professionals about the risks and benefits of medicines, medical devices and blood components, leading to safer and more effective use
- supporting innovation and research and development that's beneficial to public health
- influencing UK, EU and international regulatory frameworks so that they're risk-proportionate and effective at protecting public health

REGULATORY REQUIREMENTS AND DIFFERENT PATHWAYS FOR REGISTRATION OF DRUG PRODUCTS IN UNITED KINGDOM

Medicines and Health products Regulatory Agency (MHRA) is the Regulatory Agency in UK. A license, also referred to as a **Marketing Authorisation**, from the MHRA is required before any medicine can be used to treat people in the UK. Once the MHRA is satisfied that the medicine works as it should, and that it is acceptably safe, it is given a Marketing Authorisation or product license.

To get a Marketing Authorisation in UK the applicant may choose any one of the four procedures those are **Centralised Procedure (CP), National Procedure (NP), Decentralised Procedure (DCP) and Mutual Recognition Procedure (MRP).**

In these procedures the Centralized Procedure is mandatory for certain types of medicines and optional for others. To get a Marketing Authorisation in UK the generic manufacturer should provide quality data, bioequivalence with EU reference product and applicable Clinical and Non-Clinical reports in CTD/eCTD format. Marketing Authorisations are be valid for five years and then may be renewed on the basis of a re-evaluation of the risk-benefit balance.

MARKETING AUTHORIZATION PROCEDURES:

There are four types of procedures that applicants can take to obtain a Marketing Authorisation. To get a marketing authorisation in United Kingdom the applicant may choose any one of the four procedures those are:

1. National Procedure.
2. Centralised Procedure.
3. Decentralized Procedure.
4. Mutual Recognition Procedure.

1. National procedure:

The MHRA is responsible for granting Marketing Authorisations for medicinal products which are placed on United Kingdom markets, except for medicinal products which are authorised under Centralised Procedure. In order to obtain a national marketing authorisation, an application must be submitted to the MHRA. Marketing Authorisations (MAs) will be valid for five years and then may be renewed on the basis of a re-evaluation of the risk-benefit balance. Once renewed, the marketing authorisation will be valid for an unlimited period unless there are justified grounds relating to pharmacovigilance, to proceed with one additional five-year renewal. In addition, the five-yearly cycle of Periodic Safety Update Reports (PSURs) with renewal has been replaced by a three-year cycle. Timelines for national procedure is 210 days from the date of submission of the MA application or dossier

2. Centralised Procedure:

The Centralised Procedure is administered by the European Medicines Agency (EMA) in London. It consists of a single application which, when approved, grants marketing authorisation for all markets within the European Union consisting of 28 countries and 3 EEA countries.

The centralized procedure is **compulsory** for:

- Human medicines containing a new active substance to treat:
  - human immunodeficiency virus (HIV) or acquired immune deficiency syndrome (AIDS);
  - cancer;
  - diabetes;
  - neurodegenerative diseases;
  - auto-immune and other immune dysfunctions;
  - viral diseases.

- Medicines derived from biotechnology processes, such as genetic engineering;
- Advanced therapy medicines, such as gene-therapy, somatic cell-therapy or tissue-engineered medicines;

- Orphan medicines (medicines for rare diseases);
- Veterinary medicines for use as growth or yield enhancers.

It is **optional** for other medicines:

- containing new active substances for indications other than those stated above;
- that are a significant therapeutic, scientific or technical innovation;
- Whose authorization would be in the interest of public or animal health at EU level.

Today, **the great majority of new, innovative medicines** pass through the centralized authorization procedure in order to be marketed in the EU.

3. Mutual Recognition Procedure: (MRP)

- Mutual recognition means that EU countries may approve the decision made about a medicinal product by another EU country.
- The majority of authorisations for generic medicines are granted through the Mutual Recognition Procedure and the Decentralised Procedure.
- Under MRP, the assessment and marketing authorisation of one Member State,(The "Reference Member State (RMS)") should be "mutually recognised" by other "Concerned Member States (CMS)". Since the introduction of the DCP, the MRP is mainly used for extending the existing marketing authorisation to other countries in what is known as the "repeat use" procedure.
- The pharmaceutical company submits their application to the country chosen to carry out the assessment work, which then approves or rejects the application. The other countries have to decide within 90 days whether they approve or reject the decision made by the original country (RMS).
- Two groups are working for the facilitation of the Mutual Recognition Procedure:
  - **CMD(h)** (Coordination Group for mutual recognition and Decentralised procedures (human)) for human medicinal products.
  - **CMD(v)** (Coordination Group for mutual recognition and Decentralised procedures (veterinary))and for veterinary medicinal products.
- If a member state cannot approve the assessment report, the summary of product characteristics, the labelling and the package leaflet on grounds of potential serious risk to human and animal health or to the environment, a prereferral procedure should be issued by the relevant Co-ordination Group.
- If the Member State(s) fail to reach an agreement during the 60-day procedure of the pre-referral, a referral to the CHMP/CVMP for arbitration may be made through its secretariat at the EMEA

Repeat Use Procedure (RUP)

One can use the mutual recognition procedure more than once to add more member states to a mutually-recognized license – this is known as a repeat-use procedure. The process for repeat use is identical to the first mutual recognition procedure.

FLOW CHART OF MUTUAL RECOGNITION PROCESS (MRP) & REPEAT USE PROCEDURE (RUP)

Approx.90 days before submission to CMS :	Applicant requests RMS to update Assessment Report (AR) and allocate procedure number
Day -14	Applicant submits the dossier to CMS. RMS circulates the AR including SmPC, PL and labelling to CMSs. Validation of the application by CMSs
Day 0	RMS starts the procedure Day 30 CMSs send their comments to the RMS, CMSs and applicant
Day 40	Applicant sends the response document to CMSs and RMS
Until Day 48	RMS evaluates and circulates a report on the applicant's response document to CMSs.
Day 55	CMSs send their remaining comments to RMS, CMS and applicant
Day 55-59	The applicant and RMS are in close contact to clarify if the procedure can be closed at day 60 or if the applicant should submit a further response at day 60.
Day 60	MRP: If CMS have no remaining comments at Day 55, the RMS closes the procedure. RUP: If no potential serious risk to public health (PSRPH) has been outlined by CMS at Day 55, the RMS closes the procedure. In case a CMS has remaining comments (MRP) or PSRPH (RUP) at Day 55, the applicant sends the response document to CMSs and RMS.
Day 60-90	The period 60-90 will only be used if a CMS has remaining comments (MRP) or PSRPH (RUP) at Day 55.
Until day 68	RMS evaluates and circulates a report on the applicant's response document to CMSs.
Day 75	CMSs send their remaining comments to RMS, CMSs and applicant
Until Day 80	A break-out session (BOS) can be organised around Day 75 (but may take place between days 73-80)
Day 85	CMSs send any remaining comments to RMS, CMS and applicant.
Day 90	CMS notify RMS and applicant of final position (and in case of negative position also the CMDh secretariat of the EMA) If consensus is reached, the RMS closes the procedure. If consensus is not reached, the points for disagreement submitted by CMSs are referred to CMDh by the RMS within 7 days after day 90
Day 150	Final position adopted by the CMDh: If consensus is reached at the level of CMDh, the RMS closes the procedure. If consensus is not reached at the level of CMDh, the RMS refers immediately the matter to EMA for CHMP arbitration
5 days after close of procedure	Applicant sends high quality national translations of SmPC, PL and labelling to CMSs.
30 days after close of procedure	Granting of national marketing authorisations in the CMSs subject to submission of acceptable translations.

4. Decentralized Procedure (DCP):

- It is applicable in cases where an authorisation does not yet exist in any of the EU Member States.
- Identical dossiers are submitted in all Member States where a marketing authorisation is sought. A Reference Member State, selected by the applicant, will prepare draft assessment documents and send them to the Concerned Member States.
- They, in turn, will either approve the assessment or the application will continue into arbitration procedures.
- The new Decentralised Procedure involves Concerned Member States at an earlier stage of the evaluation than under the MRP in an effort to minimise disagreements and to facilitate the application for marketing authorisation in as many markets as possible.
- The applicant may request one or more concerned Member State(s) to approve a draft assessment report, summary of product characteristics, labelling and package leaflet as proposed by the chosen reference Member State in 210 days.

Flow Chart of the Decentralised Procedure

Pre-procedural Step	
Before Day -14	Applicant discussions with RMS RMS allocates procedure number. Creation in CTS.
Day –14	Submission of the dossier to the RMS and CMSs Validation of the application. Positive validation should only be indicated in CTS, not via e-mail.
Assessment step I	
Day 0	RMS starts the procedure. The CMS are informed via CTS.
Day 70	RMS forwards the Preliminary Assessment Report (PrAR) (including comments on SmPC, PL and labelling) on the dossier to the CMSs and the applicant Until
Day 100	CMSs send their comments to the RMS, CMSs and applicant. It may also be sufficient for the CMS to indicate in CTS only in case there are no additional comments
Until Day 105	Consultation between RMS and CMSs and applicant. If consensus not reached RMS stops the clock to allow applicant to supplement the dossier and respond to the questions.
Clock-off period	Applicant may send draft responses to the RMS and agrees the date with the RMS for submission of the final response. Applicant sends the final response document to the RMS and CMSs within a period of 3 months, which can be extended by a further 3 months.
Day 106	RMS restarts the procedure following the receipt of a valid response or expiry of the agreed clock-stop period if a response has not been received. The CMS are informed via e-mail and CTS will be updated accordingly.
Assessment step II	
Day 120 (Day 0)	RMS sends the DAR, draft SmPC, draft labelling and draft PL to CMSs and the applicant

Day 145 (Day 25)	CMSs send comments to RMS, CMSs and the applicant. It may also be sufficient for the CMS to indicate in CTS only in case there are no additional comments.
Day 150 (Day 30)	RMS may close procedure if consensus reached Proceed to national 30 days step for granting MA
Day 160	Applicant sends the response document to CMSs and RMS
Until 180 (Day 60)	If consensus is not reached by day 150, RMS to communicate outstanding issues with applicant, receive any additional clarification, prepare a short report and forward it to the CMSs and the applicant
Day 195 (at the latest)	A Break-Out Session (BOS) may be held at the European Medicines Agency with the involved MSs to reach consensus on the major outstanding issues
Between Day 195 & Day 210	RMS consults with the CMSs and the applicant to discuss the remaining comments raised.
Day 210 (Day 90)	If consensus is reached: - In case of positive position from RMS, Closure of the procedure including CMSs approval of assessment report, SmPC, labelling and PL and proceed to national 30 days step for granting the MA. - In case of negative position from the RMS, Closure of the procedure negatively. The End of Procedure letter plus final Day 210 overview AR is circulated. If consensus is not reached: In case of negative position from CMS, CMS notify the RMS, the other CMSs, applicant and the secretariat of the Co-ordination group. Referral to the Co-ordination group.
At the latest, within 7 days after Day 210)	If consensus on a positive RMS AR was not reached at day 210, the points of disagreement submitted by CMS will be referred by the RMS to the Co-ordination group for resolution
Day 270 (at the latest)	Final position adopted by Co-ordination Group with referral to CHMP/CVMP for arbitration in case of unsolved disagreement
National step	
7 days after close of procedure	Applicant sends high quality national translations of SmPC, labelling and PL to CMSs and RMS
30 days after close of the procedure	Granting of national marketing authorisation in RMS and CMSs if outcome is positive and there is no referral to the Co-ordination group. (National Agencies will adopt the decision and will issue the marketing authorisation subject to submission of acceptable translations).
30 days after close of CMD referral procedure	Granting of national marketing authorisation in RMS and CMSs if positive conclusion by the Co-ordination group and no referral to the CHMP/CVMP. (National Agencies will adopt the decision and will issue the marketing authorisation subject to submission of acceptable translations).

Fast track of Marketing Authorization:

Applications can be fast tracked if there is compelling evidence to show that the product would provide a major breakthrough in the treatment of certain conditions. There is no additional fee for fast-tracking applications.

The disease categories for which fast tracking of applications may be applicable are:

- chronic, debilitating diseases for which available treatments are ineffective or otherwise inadequate
- severe or life-threatening diseases for which available treatments are ineffective or otherwise inadequate
- the emergence of a disease with wide-spread resistance to treatment with currently available treatments
- the emergence of a new disease entity which has severe or life-threatening effects and for which currently available treatments are ineffective or inadequate

Types of application (legal basis)

You must include the appropriate legal basis for your application when you apply to MHRA for a marketing authorization:

- full application - Article 8(3)
- generic, hybrid or similar biological applications - Article 10
- well-established use application - Article 10a
- fixed combination application - Article 10b
- informed consent application- Article 10c

Certain types of application can use the abridged application procedure. This means the application does not need full pre-clinical or clinical studies. The types of application that may be able to use this route are generic/biosimilars (Article 10), well-established use (Article 10(a)) and informed consent (Article 10(c)) applications.

Guidance on Procedure for Market authorization, Presentation and content of the dossier and Regulatory Guideline can be found @ https://ec.europa.eu/health/documents/eudralex/vol-2_en

DATA EXCLUSIVITY AND MARKET PROTECTION:

Data exclusivity and market protection period for reference medicinal products:

The **period of eight years** from initial authorisation of the reference product provides a period of so-called "**data exclusivity**", after which valid applications for generic products can be submitted and lead to the granting of a marketing authorisation.

The **period of ten years** from initial authorisation of the reference product provides a period of so-called "**market protection**" after which generic products authorised in this way can be placed on the market.

One year of additional marketing exclusivity, **for a new indication**, meeting certain conditions.

VARIATIONS TO MARKET AUTHORIZATIONS:

A variation to the terms of a marketing authorization is an amendment to the contents of the documents of the approved dossier.

Variations are broadly categorized into Minor & Major.

- Minor Variations : Type IA
  Type IB
- Major Variation : Type II

Type IA variations:

Type IA variations are the minor variations which have **only a minimal impact or no impact at all**, on the quality, safety or efficacy of the medicinal product, and **do not require prior approval before implementation ("Do and Tell" procedure).**

Such a minor variations are "classified" two subcategories, which impact on their submission:

A) Type lA variations requiring immediate notification ('IA IN'):

Type IA variations must be notified (submitted) immediately to the National Competent Authorities/European Medicines Agency ('the Agency') following implementation, in order to ensure the continuous supervision of the medicinal product.

Examples of Type IAIN variation:

- Change in the name and/or address of the marketing authorization holder
- Change in the name and/or address of a manufacturer/importer of the finished product (including batch release or quality control testing sites)
- Changes in imprints, bossing or other markings
- Change in the shape or dimensions of the pharmaceutical form particularly Immediate release tablets, capsules, suppositories and pessaries.

B) Type lA variations NOT requiring immediate notification ('IA'):

Variations which do not require immediate notification may be submitted by the marketing authorisation holder (MAH) within 12 months after implementation, or may be submitted earlier should this facilitate dossier life-cycle maintenance or when necessary.

Examples of Type IA variation:

- Addition of physico-chemical test in specification.
- Deletion of non-significant test (ex: Identification test in Stability study).
- Tightening of specification limits (ex: Tightening of test limit for water content, Residual solvents and Related substances..etc.
- CEP updates/renewal.
- API and FP Batch size increase/decrease within 10 fold.

Type IB variations:

- Commission Regulation (EC) No 1234/2008 ('the Variations Regulation') defines a minor variation or Type 1B as a variation which is neither a Type lA variation nor Type II variation nor an Extension.
- Such minor variations must be notified to the National Competent Authority/European Medicines Agency by the Marketing Authorisation Holder (MAH) before implementation, but do not require a formal approval.
- However, the MAH must wait a period of 30 days to ensure that the
- Post-Authorisation procedural advice for users of the centralised procedure notification is acceptable by the Agency before implementing the change **(Tell, Wait and Do procedure).**

Examples of Type IB Variations

- Major change the approved Analytical method
- FP Mfg. site changes
- Shelf-life extension
- Change in storage condition
- Minor changes to approved manufacturing process
- Change in batch size beyond 10 fold category
- SmPC /PIL changes in-line with innovator product

Type II variations:

Commission Regulation (EC) No 1234/2008 ('the Variations Regulation') defines a major variation of Type II as a variation which is not an extension of the Marketing Authorisation (line extension) and that may have a significant impact on the quality, safety or efficacy of a medicinal product.

Examples of Type II Variations

- Addition of alternate/new API DMF supplier
- Relaxation of approved specification
- Major change in approved manufacturing process
- Major change in approved composition

Current MHRA fees

Statutory guidance to current MHRA fee can be identified at

https://www.gov.uk/government/publications/mhra-fees/current-mhra-fees#licence-applications-marketing-authorisations-including-extension-applications-fees

LICENCE APPLICATIONS: MARKETING AUTHORISATIONS FEES (INCLUDING EXTENSION APPLICATIONS)

Major	
National fee (including hybrid applications)	£92,753
Decentralised procedure where the UK is a concerned member state (CMS)	£89,556
Major (reduced in exceptional circumstances or orders under Section 104/105)	£29,732
Outgoing mutual recognition where the UK is the reference member state (RMS)	
1st wave	£41,573
2nd wave	£27,308
Incoming mutual recognition with the UK as a CMS and European reference products	£62,421
Abridged complex	
National fee (including hybrid applications)	£25,643
Decentralised procedure where the UK is a concerned member state (CMS)	£24,760
Outgoing mutual recognition where the UK is the reference member state (RMS)	
1st wave	£10,753
2nd wave	£7,133
Incoming mutual recognition (UK CMS) and European reference products	£17,330
Abridged standard	
National fee	£9,402
Decentralised procedure (UK CMS)	£9,078
Outgoing mutual recognition (UK RMS)	
1st wave	£4,282
2nd wave	£3,567
Incoming mutual recognition (UK CMS) and European reference products	£6,350
Abridged simple	
National fee	£2,564
Decentralised procedure where the UK is a CMS	£2,564
Outgoing mutual recognition where the UK is an RMS	£2,564
Outgoing mutual recognition (informed consent)	£2,564
1st wave	£2,564
2nd wave	£2,564
Duplicates for all of the above outgoing mutual recognition applications when undertaken at the same time as the lead application	£2,564

Decentralised procedure where UK is RMS

Major	£121,664
Abridged complex	£35,634
Abridged standard	£15,659
Abridged simple	£8,105
Extension application	
Extension application group (National fee)	£25,643
Extension application group bulk (National fee)	£9,402
Abridged standard	
National fee	£9,402
Decentralised procedure (UK CMS)	£9,078
Outgoing mutual recognition (UK RMS)	
1st wave	£4,282
2nd wave	£3,567
Incoming mutual recognition (UK CMS) and European reference products	£6,350
Extension application group	
Decentralised procedure where the UK is RMS	£35,634
Decentralised procedure where the UK is CMS	£24,760
Outgoing mutual recognition (UK RMS)	
1st wave	£10,753
2nd wave	£7,133
Incoming mutual recognition (UK CMS)	£17,330
Extension application group bulk	
Decentralised procedure where the UK is RMS	£15,659
Decentralised procedure where the UK is CMS	£9,078
Outgoing mutual recognition (UK RMS)	
1st wave	£4,282
2nd wave	£3,567
Incoming mutual recognition (UK CMS)	£6,350
(To which Section G of Part IV of the Annex to Council Directive 75/318/EEC refers)	
Parallel import complex application (2)	£18,180
Standard application (2)	£6,663
Simple application	£1,792
Change of ownership (including THMPD registrations)	£442
Manufacturers' licences (including THMPD and homeopathic medicinal products	
Standard (3)	£3,143
Non-orthodox practitioner (NOP)	£183
Change of ownership	£344

EFFECT OF BREXTI:

On 29 March 2017, the United Kingdom (UK) notified the European Council of its intention to withdraw from the European Union (EU), a process known as 'Brexit'. Brexit will be effective from **30 March 2019**

Critics feel BREXIT might not cause much disruption to the European pharmaceutical industry, as they believe it is unlikely that the UK will sever its ties with the EMA, despite the vote to leave the EU. There are also concerns that if the UK cuts all ties with the EU, then it may have to develop its own domestic regulatory system, leading to further confusion for companies looking to obtain drug approvals in both the UK and the EU. One of the potential solutions would be for the MHRA to function like Switzerland's regulator, Swissmedic, where medical products are independently authorized but work with EMA is conducted under mutual recognition and sharing agreements.

The second solution would be that the UK's MHRA could function like other regulators in Norway, Iceland and Liechtenstein, which have adopted the complete EU acquisition on medicinal products, and are consequently parties to the centralized procedure. The UK will look to follow either the first or second of potential scenarios - which one will depend on the terms of the country's exit from the EU.

USFDA has entered mutual regulatory recognition with 8 of top EU countries (UK is one of them) trade between them happens at faster pace.

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Details of importing country embassy in India: **https://www.gov.uk/world/organisations/british-high-commission-new-delhi**

Contact details of Indian Embassy abroad: **https://www.hcilondon.in/**

List of Local Pharma Associations:

- Association of the British Pharmaceutical Industry (ABPI), Ms. Lisa Anson, President, 7th floor, Southside, 105 Victoria Street, London ,SW1E 6QT. — Ph:(+)44 (0) 20 7930 3477 Website: www.abpi.org.uka -
- British Generic Manufacturers Association (BGMA) — Website: http://www.britishgenerics.co.uk/