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Der Pharmacia Lettre, 2015, 7 (3):188-195
(http://scholarsresearchlibrary.com/archive.html)

ISSN 0975-5071
USA CODEN: DPLEB4

Regulatory requirements and different pathways for registration of drug products in united kingdam

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ABSTRACT

This aim of present work to understand the requirements for preparation and compilation of dossier for prescription drugs (Generics) in United Kingdom (UK) and also to facilitate a brief overview of Marketing Authorisation procedures in UK. 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. There are four types of procedures that applicants can take to obtain a Marketing Authorisation. 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. Under the medicines legislation which was implemented on the 30 October 2005, 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.

Key words: MHRA, Generics, Marketing Authorisation, CTD, Drug Product.

INTRODUCTION

Dossier is a collection of papers giving detailed information about a particular person or subject. (or) a bundle of papers in reference to some matter or relating to a person [1]. (or) Dossier is a file document submitted to the Regulatory Authorities which contains detailed information about the drug product.

In United Kingdom all drug products are classified into 3 categories based on their safety profile. Prescription only medicines (POM), Supervision of Pharmacist (P) and General Sale List (GSL).

New medicines are usually authorized for use as Prescription Only Medicines (POM). After some years use, if adverse reactions to the medicine are few and minor, it is possible that the medicine may be safely used without a doctor's supervision. If there is sufficient evidence of safety, a medicine may be reclassified for sale or supply under the supervision of a Pharmacist (P). Pharmacy medicines which have been safely used for several years may be suitable for General Sale and may be reclassified as GSL [2].

The Medicines and Healthcare products Regulatory Agency (MHRA) is the regulatory agency in United Kingdom. MHRA is a government body which was set up in 2003 to bring together the functions of the Medicines Control Agency (MCA) and the Medical Devices Agency (MDA) [3]. These include the regulation of medicines and medical devices and equipment used in Healthcare and the investigation of harmful incidents.

A license, also referred to as a Marketing Authorization (MA), from the MHRA is required before any medicine can be used to treat people in the UK. Licenses for medicines are granted only when a product meets high standards of quality, safety and works for the purpose intended (efficacy).

There are four types of procedures that applicants can take to obtain a Marketing Authorisation. 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) [4]. In these procedures the Centralized Procedure is mandatory for certain types of medicines and optional for others. 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. CP is mandatory for Biotechnological Products and New Active substances for which the therapeutic indication is the treatment of AIDS, Cancer, Diabetes, Neurodegenerative disorder and Orphan products.

In cases where national authorisations are requested for the same medicinal product in more than one Member State and the marketing authorisation holder has received a marketing authorisation in a Member State, the applicant/marketing authorization holder shall submit an application in the Member States concerned using the procedure of mutual recognition. If no marketing authorisation has been granted in the Community, the applicant may make use of a decentralised procedure and submit an application in all the Member States where it intends to obtain a marketing authorisation at the same time, and choose one of them as reference Member State.

In order to obtain a national marketing authorisation, an application must be submitted to the MHRA. 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.

To get a Marketing Authorisation in UK the generic manufacturer should provide a Dossier with quality data, bioequivalence with EU reference product and applicable Clinical and Non-Clinical reports in CTD/eCTD format. In assembling the dossier for application for Marketing Authorisation, applicants shall also take into account the scientific guidelines relating to the quality medicinal products for human use as adopted by the Committee for Medicinal Products for Human Use (CHMP) and published by the European Medicine Evaluation Agency (EMEA). All data should be submitted following the relevant headings of the EU-CTD according to Notice to Applicants (NTA), Volume 2B [5].

The safe use of all medicines depends on users reading the labelling and packaging carefully and accurately and being able to assimilate and act on the information presented. The primary purpose of medicines labelling and packaging should be the clear unambiguous identification of the medicine and the conditions for its safe use. So the labelling requirements must have been followed by the applicant while preparing the drug product label[6].

The purpose of establishing bioequivalence is to demonstrate equivalence in Bio-pharmaceutics quality between the generic medicinal product and a reference medicinal product in order to allow bridging of preclinical tests and of clinical trials associated with the reference medicinal product. So bioequivalence with reference medicinal product is required for a drug product and the data of bioequivalence should be included in a dossier [7].

Under the new medicines legislation which was implemented on 30 October 2005, 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 [8].

MATERIALS AND METHODS

Literature review was done mainly on collection of European Medicines Agency (EMA) legislations, United Kingdom member state concentrating on their generic drug registration procedures.

The research carried out with the collected data by analysing the terms of the below parameters:

Types of study:

The study was conducted with an objective to chalk out the regulatory framework for generic drug registration legislations and guidelines. The major emphasis has been provided to regulatory requirements of United Kingdom.

Source of data:

Major part of secondary data collection was done by means of following sources

Literature review:
Typically covered the books and regulatory guidelines published officially by government authorities, including the academic journals, online journals, market research reports and other resources.

Internet using the web page content:
The literature was collected using numerous search engines e.g. Pharmabiz, RAPS, RAJ Pharma, Google Scholar and others website. Online books also served as a good source of information. Key words in the search involved generic drug registration requirements along with the name of various parameters associated to pharmaceutical field, name of regulatory bodies and other variations were used.

Criteria for selection of study parameters:
Requirement for filing MA application:
Application for generic drug registration should be in local language of country i.e. English, in which we need to fill all the details of generic drug product, type of MA submission.

RESULT AND DISCUSSION

Regulatory authority:
The Medicines and Healthcare products Regulatory Agency (MHRA) is the regulatory agency in United Kingdom.

MHRA is a government body which was set up in 2003 to bring together the functions of the Medicines Control Agency (MCA) and the Medical Devices Agency (MDA). These include the regulation of medicines and medical devices and equipment used in Healthcare and the investigation of harmful incidents. The MHRA also looks after blood and blood products, working with UK blood services, healthcare providers, and other relevant organisations to improve blood quality and safety.

Requirements for registration of medicinal products in the United Kingdom:
A license, also referred to as a Marketing Authorization (MA), from the MHRA is required before any medicine can be used to treat people in the UK. Licenses for medicines are granted only when a product meets high standards of quality, safety and works for the purpose intended (efficacy). The regulatory system also imposes rigorous standards on medicines manufacturers and wholesale dealers who trade in them. The licensing system guarantees accountability for all those involved and ensures that processes, supplies, and quality can be thoroughly monitored and swift corrective action taken where necessary. The authorization process for devices differs from that applied to medicines. However, once marketed, safety and performance of medicines and medical devices are monitored and enforced in similar ways.

To begin the process, companies and/or researchers must apply to the MHRA for permission to test drugs through clinical trials, if these trials are to be conducted in the UK. In order to receive permission to run a trial, they must first satisfy the MHRA that they have met strict safety criteria. All the test results from these trials on how well the medicine works and its side effects, plus details of what the medicine contains, how it works in the body, and who it is meant to treat, are then sent to the MHRA for detailed assessment. The assessment team is made up of experts from different relevant specialties, each of whom has undergone additional training in medicines assessment.

The length of the assessment process depends on the type of medicine as well as the quality of the initial information supplied by the manufacturer, how much further detail is required, and how soon queries can be resolved. In the past, all this information used to be supplied in paper format; now it is supplied electronically, to minimize procedural delays. MHRA also has to comply with strict timeframes and performance targets for the licensing of medicines.

Once the MHRA is satisfied that the medicine works as it should, and that it is acceptably safe, it is given a marketing authorization or product license. The pharmaceutical company and any wholesalers must also be able to satisfy the MHRA that the manufacture, distribution, and supply of the medicine meet the required safety and quality standards.

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. Under the new medicines legislation which was implemented on 30 October 2005, 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 [9].

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 [10].

3. Mutual Recognition Procedure: (MRP)
1. Mutual recognition means that EU countries may approve the decision made about a medicinal product by another EU country.
2. The majority of authorisations for generic medicines are granted through theMutual Recognition Procedure and the Decentralised Procedure.
3. 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.
4. 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).
5. Two groups are working for the facilitation of the Mutual Recognition Procedure: for human medicinal products, the CMD (h) (Coordination Group for mutual recognition and Decentralised procedures (human)), and for veterinary medicinal products, the CMD (v) (Coordination Group for mutual recognition and Decentralised procedures (veterinary)).
6. 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 pre-referral procedure should be issued by the relevant Co-ordination Group.
7. 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 [11].

Table No 1: Mutual Recognition Procedure with timelines

Day	Progress
Pre submission:	
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 SPC, PL and labelling to CMSs. Validation of the application in the CMSs.
Post submission:	
Day 0	RMS starts the procedure
Day 50	CMSs send their comments to the RMS and applicant
Day 60	Applicant sends the response document to CMSs and RMS
Until Day 68	RMS circulates their assessment of the response document to CMSs.
Day 75	CMSs send their remaining comments to RMS and applicant. A break-out session can be organised between days 73 – 80.
Day 85	CMSs send any remaining comments to RMS and applicant.
Day 90	CMSs notify RMS and applicant of final position (and in case of negative position also the CMD secretariat of the EMEA). If consensus is reached, the RMS closes the procedure. If consensus is not reached, the points for disagreement submitted by CMS(s) are referred to CMD (h) by the RMS within 7 days after Day 90.
Day 150	For procedures referred to CMD(h): If consensus is reached at the level of CMD(h), the RMS closes the procedure. If consensus is not reached at the level of CMD(h), the RMS refers the matter to CHMP for arbitration

5 days after close of procedure	Applicant sends high quality national translations of SPC, PL and labelling to CMSs and RMS.
30 days after close of procedure	Granting of national marketing authorisations in the CMSs subject to submission of acceptable translations.

4. Decentralized Procedure (DCP):

1. The Decentralised procedure came into operation in late 2005. It is applicable in cases where an authorisation does not yet exist in any of the EU Member States.
2. 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.
3. They, in turn, will either approve the assessment or the application will continue into arbitration procedures.
4. 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.
5. 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.

Table No 2: Decentralized Procedure with timelines

Day	Progress
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
Assessment step I	
Day 0	RMS starts the procedure
Day 70	RMS forwards the Preliminary Assessment Report (PAR),SPC , PL and labelling to the CMSs
Until Day 100	CMSs send their comments to the RMS
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 recommended period of 3 months, which could be extended if justified
Day 106	Valid submission of the response of the applicant received. RMS restarts the procedure
Day 106 – 120	RMS updates PAR to prepare Draft Assessment Report (DAR) draft SPC, draft labelling and draft PIL to CMSs.
Day 120	RMS may close procedure if consensus reached. Proceed to national 30 days step for granting MA.
Assessment step II	
Day 120 (Day 0)	If consensus not reached RMS sends the DAR, draft SPC, draft labelling and draft PIL to CMSs
Day 145 (Day 25)	CMSs sends final comments to RMS
Day 150 (Day 30)	RMS may close procedure if consensus reached Proceed to national 30 days step for granting MA
Until 180 (Day 60)	If consensus is not reached by day 150, RMS to communicate outstanding issues with applicant, receive any additional clarification and prepare a short report for discussion at Coordination Group.
Until Day 205 (Day85)	Breakout Group of involved Member States reaches consensus on the matter.
Day 210 (Day 90)	Closure of the procedure including CMSs approval of assessment report, SPC, labelling and PIL, or referral to Co -ordination group. Proceed to national 30 days step for granting MA.
Day 210 (at the latest)	If consensus was not reached at day 210, points of disagreement will be referred 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	
Day 110/125/155/215/275	Applicant sends high quality national translations of SPC, labelling and PIL to CMS and RMS
Day 135/150/180/240	Granting of national marketing authorisation in RMS and CMSs if 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).
Day 300	Granting of national marketing authorisation in RMS and CMSs if positive conclusion by the Coordination 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).

The two groups, CMD(h) and CMD (v), also work for the facilitation of the decentralised procedures. 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 pre-referral procedure should be issued by the relevant Coordination 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 [12].

Requirements for dossier preparation and compilation.

Dossier requirements

1. Quality requirements
2. Labelling requirements
3. Bioequivalence requirements

1. Quality requirements[5]:

- In assembling the dossier for application for Marketing Authorisation, applicants shall also take into account the scientific guidelines relating to the quality medicinal products for human use as adopted by the [Committee for Medicinal Products for Human Use (CHMP) and published by the European Medicine Evaluation Agency (EMEA).
- All data should be submitted following the relevant headings of the EU-CTD according to Notice to Applicants (NTA), Volume 2B.
- With respect to the quality part (chemical, pharmaceutical and biological) of the dossier, all monographs including general monographs and general chapters of the European Pharmacopoeia are applicable.
- The manufacturing process shall comply with the requirements of Commission Directive 91/356/EEC laying down the principles and guidelines of Good Manufacturing Practice (GMP) for medicinal products for human use (2) and with the principles and guidelines on GMP, published by the Commission in The rules governing medicinal products in the European Community, Volume 4.
- With regards to quality (Q) data, this type of submission should include at least general information and information related to the starting and raw materials, manufacturing process of the active substance(s), data on characterisation of the active substance(s) (limited to the data necessary to 5/22 adequately describe the active substance(s)), control of substance(s), and description and composition of the finished medicinal product.
- When further developing the manufacturing process, the product development will have evolved to a stage where significant improvement have been achieved, e.g. the reproducibility of the manufacturing process has been addressed, characterisation of the substance/medicinal product has been performed and where interim specification have been set. At such a point, a follow up on Q or Q and NC certification can be submitted.

2. Labelling requirements[6]:

The safe use of all medicines depends on users reading the labelling and packaging carefully and accurately and being able to assimilate and act on the information presented. The primary purpose of medicines labelling and packaging should be the clear unambiguous identification of the medicine and the conditions for its safe use. Common factors affecting all users of medicines may be summarised under three headings:

✓ **Information**: Certain items of information are vital for the safe use of the medicine.

✓ **Format**: The information must be presented in a legible manner that is easily understood by all those involved in the supply and use of the medicine.

✓ **Style**: There is potential for confusion between both similarity in drug names and similarity in medicines packaging.

General considerations:

Labelling must contain *all* elements required by article 54 of Council Directive 2001/83/EEC. Nevertheless, certain items of information are deemed critical for the safe use of the medicine.These items are**:** Name of the medicine**,** Expression of strength (where relevant)**,** Route of administration**,** Posology**,** Warnings.

3. Bioequivalence requirements[7]:

✓ Two medicinal products containing the same active substance are considered bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives and their bio availabilities (rate and extent) after administration in the same molar dose lie within acceptable predefined limits.

✓ In bioequivalence studies, the plasma concentration time curve is generally used to assess the rate and extent of absorption.

✓ Selected pharmacokinetic parameters and preset acceptance limits allow the final decision on bioequivalence of the tested products.

✓ AUC, the area under the concentration time curve, reflects the extent of exposure. Cmax, the maximum plasma concentration or peak exposure, and the time to maximum plasma concentration, tmax , are parameters that are influenced by absorption rate.

Generic medicinal products:

✓ In applications for generic medicinal products according to Directive 2001/83/EC, Article 10(1), the concept of bioequivalence is fundamental.

✓ The purpose of establishing bioequivalence is to demonstrate equivalence in biopharmaceutics quality between the generic medicinal product and a reference medicinal product in order to allow bridging of preclinical tests and of clinical trials associated with the reference medicinal product.

The different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance are considered to be the same active substance, unless they differ significantly in properties with regard to safety and/or efficacy. Furthermore, the various immediate-release oral pharmaceutical forms shall be considered to be one and the same pharmaceutical form.

FEES:

Table No 3: Fees for licence applications from 1 April 2014 [13]

licence applications	Fee £
Major	
National fee (Including hybrid applications)	103,059
Decentralised procedure where UK is CMS	99,507
Major (reduced in exceptional circumstances1 or orders under Section 104/105)	33,035
Outgoing Mutual Recognition (UK RMS)	
- 1st wave	46,192
- 2nd wave	30,342
Incoming Mutual Recognition (UK CMS) and European reference products	69,357
Abridged complex	
National fee (including hybrid applications)	28,492
Decentralised procedure where UK is CMS	27,511
Outgoing Mutual Recognition (UK RMS)	
- 1st wave	11,948
- 2nd wave	7,925
Incoming Mutual Recognition (UK CMS)and European reference products	19,256
Abridged standard	
National fee	10,447*
Decentralised procedure where UK is CMS	10,087
Outgoing Mutual Recognition (UK RMS)	
- 1st wave	4,758
- 2nd wave	3,963
Incoming Mutual Recognition (UK CMS)and European reference products	7,056
Abridged simple	
National fee	2,849
Decentralised procedure where UK is CMS	2,849
Outgoing Mutual Recognition (UK RMS)	2,849
Outgoing Mutual Recognition(informed consent)	2,849
- 1st wave	2,849
- 2nd wave	2,849
Duplicates for all of the above **outgoing Mutual Recognition applications** when undertaken at the same time as the lead application	2,849
Decentralised procedure where UK is RMS	
Major	143,134
Abridged complex	41,922
Abridged standard	18,422*
Abridged simple	9,535

CONCLUSION

United Kingdom has a major marketing value for pharmaceuticals it is one of the top ten major pharmaceutical markets. Present study is explained in brief about the Marketing Authorisation procedures and Dossier requirements i.e, Quality requirements, Bioequivalence and Labelling requirements for a prescription drugs (generics). So by knowing the Regulatory landscape of this Region it is helpful in getting a marketing authorization from MHRA.

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