Review Article

Marketing Authorisation Procedures in Europe: A Regulatory Perspective

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Abstract

Background: European Union (EU) is a hub of political and economic union of 27 member states (MS) and extensive amount of effort was spent by the EU Commission, the EU parliament, the EMEA and the national authorities in updating the EU regulatory environment for pharmaceuticals and granting marketing authorisations within the EU.

Methodology/Principal Findings: There are three procedures by which a marketing authorisation in EU can be obtained, Centralised Procedure which is compulsory for any novel medicinal products, subject to agreement by Committee on Proprietary Medicinal Products (CPMP), Mutual Recognition Procedure (MRP) which commences only after a marketing authorisation has been issued in a EU MS, which then becomes the Reference Member State (RMS) and the Decentralised Procedure which came into force with the newly revised EU pharmaceutical Directive in November 2005 which is applicable in cases where an authorisation does not yet exist in any of the EU Member States.

Conclusions/Significance: Even if the European directive is completely implemented, the harmonisation process appears difficult in consideration of the different social, political and economical characteristics of the different countries and this paper aims at differentiating the different marketing submissions in EU.

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Key words: European Union; Centralised Procedure; Mutual Recognition Procedure; Decentralised Procedure

1. Introduction:

In the light of European Union (EU) as an economic and political union of 27 member states located primarily in Europe, extensive amount of effort was spent by the EU Commission, the EU parliament, the European Medicines Agency (EMEA) and the national authorities in updating the EU regulatory environment for pharmaceuticals. [1,2] The European Community Directives in the field of medicinal products have the primary purpose to safe-guard public health and to eliminate the disparities liable to affect the common market, without hindering the development of the pharmaceutical industry. In order to obtain a marketing authorisation by the European Commission for a product to be simultaneously valid in all member states of the European Union and recognized by the states of the European Economic Area (EEA), an application must be submitted through the centralised procedure to the European Medicines Agency (European Agency for Evaluation of Medicinal
Products; EMEA). This marketing authorisation procedure for medicinal products for human use is currently governed by Regulation (EC) 726/2004 (1), and the marketing authorisation granted by the European Commission is based on a scientific opinion from the EMEA’s Committee for Medicinal Products for Human Use (CHMP) [3].

In the European Community many problems have arisen in connection with the free circulation of medicinal products due to different national procedures for marketing authorisation. [4] Medicinal products containing new active substances may be granted a marketing authorisation in the EU only when the applicant pharmaceutical company has provided data which are considered to satisfactorily support the quality, safety and efficacy of the product. [5] In this paper we consider the influence of the new procedures and the problems faced for obtaining the marketing authorisation of the medicinal product.

2. Rest of the Review Article:
2.1 New Procedures for Obtaining a Marketing Authorisation in European Union:
Until the end of December 1997, it was still possible for companies to make separate applications for licensure of a new active substance to some or all of the national licensing authorities in individual EU Member State (MS). Since each national assessment was conducted in isolation, the Summary of Product Characteristics (SPC) in use in each country was usually different in at least some respects from those of other MS in which the same active substance was licensed. [5]

According to European Generic Medicines Association (EGA), the marketing authorisation for a pharmaceutical product in more than one country in the European Union must currently be applied for through one of two procedures: either the “Centralised Procedure” or the “Mutual Recognition Procedure” (MRP). A third, the “Decentralised Procedure,” came into force with the newly revised EU pharmaceutical Directive in November 2005. [6]

2.2 The Centralised Procedure:
The centralized procedure [4,5] is the evolution of the concentration procedure. [4,6] The Centralised Procedure is administered by the European Medicines Agency (EMEA) in London. It consists of a single application which, when approved, grants marketing authorisation for all markets within the European Union. This procedure is obligatory for high-tech and biotechnology-derived products, for products used for the rare diseases (so called orphan products), and for products used for treating Acquired Immune Deficiency Syndrome (AIDS), cancer, neurodegenerative disorders and diabetes, as well as for auto-immune and viral diseases since May 2008. This procedure may also be used for authorisation of products with new active substances and for all other products bringing therapeutic or scientific progress and which are important for patients and animals at the Community level. This procedure may also be used for generic medicines applications once the data exclusivity periods granted to originator products authorized through this procedure begin to expire. [7]

After notifying the European Agency for the Evaluation of Medicinal Products (EMEA) of intent to use the procedure, the CPMP must give consent and appoint the Rapporteur and Co-Rapporteur. These are two individual CPMP members from different EU MS whose appointment may or may not fit in with the applicant’s preferences for Rapporteurs. The clock starts at the CPMP meeting which follows validation of the dossier by the EMEA and delivery to the Rapporteurs. (Figure 1) [7,8]

The two Rapporteurs draw on the expertise of their national agency staff and/or appropriate experts in the field to prepare the two quite separate assessment reports within 70 days. Each report makes a provisional recommendation regarding whether or not marketing authorisation may be granted and, if necessary, lists any Major Objections which would preclude licensure if not resolvable. There is also a list of Points for Clarification which must be addressed by the applicant before a final opinion is reached, together with a list of recommendations for modification of the SPC, Patient Information Leaflet (PIL) and labeling. All CPMP members, the EMEA and the applicant are sent the two assessment reports; CPMP members have 30 days to comment. After CPMP discussion and agreement, with or without modification, on the content of this document, it is sent to the applicant and the clock is stopped at day 120. The applicant must respond within 6 months. On re-starting of the clock, the Rapporteurs prepare a Joint Assessment Report within 30 days and CPMP have 20 days to comment. CPMP considers the application (day 180) when it is possible for an opinion to be reached. [8]

However, if there are outstanding issues which need to be addressed (with or without a hearing), these are communicated to the applicant and the opinion deferred. With or without a further clock stop, an opinion must be reached within 210 ‘clock-on’ days. If the opinion is positive, the marketing authorisation is subsequently issued by the European Commission and the European Public Assessment Report (EPAR) is placed in the public domain. This contains a brief overview of all the scientific data which supported the CPMP decision. [9]

2.3 The Mutual Recognition Procedure (MRP):
The Mutual Recognition Facilitation Group started its work in 1995 as an informal group. With the adoption of Directive 2004/27/EC the Mutual Recognition Facilitation Group has an official status and is renamed as coordination group. [10]
The MRP is to be used if the aim is to register in more than
Notification to EMEA
Appointment of Rapporteur and Co-Rapporteur (from different EU MS)
CPMP meeting, validation of dossier by EMEA and delivery to Rapporteurs
Preparation of two separate assessment reports by the Rapporteurs
Reports sent to all CPMP members, EMEA and applicant
Comment of CPMP members
Reports sent to applicant with or without modification by CPMP
Response by the applicant
Preparation of Joint assessment report by the Rapporteurs
Comments of CPMP
Any outstanding issues communicated to applicant and opinion is deferred by CPMP
CPMP Opinion
Assessment report to Commission
If positive opinion by CPMP, then marketing authorisation is issued

Fig 1: Centralization Procedure
Entire dossier sent by the applicant to all the CMS while assessment reports sent by RMS to all CMS and Applicant

CMS receive documents and validated dossier

Each country notify RMS and applicant of any major objections

Preparation and circulation of rapid response and amendment of SPC (as necessary) by the applicant

Meeting held between RMS and CMS at the EMEA

Resolution of all outstanding objections

CMS issue individual national authorisations

Any CMS still refuse to accept marketing authorisation on day 90, the applicant may withdraw the application from one or more countries

Fig 2: Mutual Recognition Procedure

one Member State and the medicinal product in question has already received a Marketing Authorisation (MA) in any MS at the time of application. The MRP is based on the idea that a national license approved in one EU Member State (Reference Member State-RMS) should be mutually recognized in other EU countries (Concerned Member States-CMS). This is based on the assumption that the evaluation criteria in the EU member states are sufficiently harmonized and are of the same standard. At the end of a MRP, national licenses are issued in the CMSs involved in the procedure.[11] (Figure 2)[7]

If initial applications were made in more than one country, any ongoing assessments must cease when the RMS authorizes the product. The Company then sends out the entire dossier to all the CMS (up to 14 EU MS plus Norway and Iceland), while the RMS sends out the assessment report to all CMS and to the applicant. The clock starts when all CMS have received these documents and validated the dossier. Each country has until day 55 to notify the RMS and applicant of any major objections to recognition of the initial marketing authorisation. The Company prepares and circulates a rapid response to any matters raised and amends the Summary of Product Characteristics (SPC) as may be necessary in order to secure a more widely acceptable version. Nevertheless, it is commonly necessary for a meeting to be held between RMS and CMS around day 75 at the EMEA in order to try to resolve outstanding matters. This may or may not involve hearing the applicant on certain points.[8]

If all outstanding objections have been resolved by day 90, the CMS issue individual national authorisations and the RMS initial SPC is modified in line with the end-of-procedure version. If any CMS still refuse to accept the marketing authorisation on day 90, and/or would accept it only after changes to the SPC which the applicant is unwilling to make, the Company may withdraw from one or
more countries. Alternatively, a process of arbitration may be triggered in which the ‘blocking’ issues to mutual recognition are listed by the countries involved. These matters are eventually considered by CPMP, whose opinion is then binding on all CMS, whatever their previous position.\[8\] The mutual recognition procedure is also applicable for extensions of existing national marketing authorisations. Before the applicant can use the mutual recognition, he has to ensure that the submitted dossiers are identical.\[10\]

It is possible to use the mutual recognition procedure more than once for subsequent applications to other MS in relation to the same medicinal product (so called repeat use). It is recommended that, wherever feasible, the marketing authorisation holder considers involving all MS where the product is intended to be marketed, in the first use of mutual recognition procedure.\[10\]

In case the applicant withdraws its application for mutual recognition during mutual recognition procedure, this does not prevent the marketing authorisation holder to initiate a second procedure of mutual recognition for that/those MS(s) at a later stage. Each subsequent procedure will be treated as a new mutual recognition procedure including the possibility for the new CMS to raise objections based on potential serious risk to public health. In the case of such a repeat use procedure, the subsequent application for mutual recognition will have to comprise the original dossier updated by any variation or renewal which had been approved and/or amended after authorisation; if necessary, additional data accepted by all MS involved in the previous procedure and a proposal for a SPC, package leaflet and labeling identical to the currently authorized. The RMS will send the original assessment report including the assessment of the updated dossier and variations as an Annexure or as an updated assessment report to the CMS.\[10\]

2.3.1 Exclusions:
The mutual recognition procedure will not be used for applications for:

- Products falling under the compulsory scope of the centralised procedure as set out in the Annexure to Regulation (EC) 726/2004 i.e.:
  i) Products developed by certain biotechnological processes,
  ii) Products containing a new active substance not authorized in the Community at the time of entry into force of the Regulation and with therapeutic indication for treatment of certain diseases,
  iii) Products designated as orphan medicinal products pursuant to Regulation (EC) 141/2001;
- Products where the company has selected to submit through the centralised procedure according to Article 3(2) and 3(3) of Regulation (EC) 726/2004, irrespective whether the marketing authorisation was granted, was rejected (negative opinion), or the applicant withdrew his application after an assessment by the EMEA of the submitted data; However, if the dossier for a withdrawn medicinal product or a medicinal product which has had a negative opinion in the centralised procedure is supplemented with new data based on new pre-clinical studies and tests and clinical trials, the application is considered to be based on a new dossier. For those applications, the applicant can apply again through centralised or mutual recognition where applicable, in those cases where a centralised procedure is not compulsory.
  - Homeopathic products referred to under Article 16(2) of Directive 2001/83/EC cf. Article 39(2) of that Directive;
  - Special, simplified registration of traditional herbal medicinal products which are not falling within the scope of Article 16d(1), cf. Article 16g(1) of Directive 2001/83/EC
  - Products falling within the transitional arrangements for Cyprus, Lithuania, Malta, Poland and Slovenia upon their accession to the EU.\[10\]

2.3.2 Extensions:
Introducing in a human medicinal product a proteinaceous component obtained through a biotechnology process listed in Annexure to Regulation (EC) 726/2004

- Referring to original medicinal products which have not been;
  i) Harmonized via national procedures,
  ii) Referred in accordance with Article 30 or 31 of Directive 2001/83/EC, or
  iii) Authorized by Member States following Directive 87/22/EEC (Ex-concertation procedure).\[10\]

2.4 The New Decentralised Procedure:
The new Decentralised came into operation in late 2005. It is applicable in cases where an authorisation does not yet exist in any of the EU MS. Identical dossiers are submitted in all MS where a marketing authorisation is sought. A RMS, selected by the applicant, will prepare draft assessment documents and send them to the CMS. They, in turn, will either approve the assessment or the applicant will continue into arbitration procedures. The new Decentralised Procedure involves CMS at an earlier stage of the evaluation than under the MRP in an effort to minimize disagreements and to facilitate the application for marketing authorisation in as many markets as possible.\[7\]
2.5 Major Hurdles:

2.5.1 Summary of Product Characteristics:
The SPC constitutes one of the major hurdles facing a generic medicine’s application for authorisation. The SPC is the information which accompanies the product.

Until 1998, originator companies submitted applications for marketing authorisation on a national basis, which gave rise to differing assessments of the same data from one country to another due to differences in local medical practices. This also explains why originators made differing applications for a product in the various countries. As a result, the dosage, uses and warnings often vary between MS. The generic medicines applicant, however, must introduce the same application file with the same SPC in all CMS, forcing a harmonisation where none existed previously.

In some cases, MS are unwilling to accept any difference between the SPC of the originator and the generic medicine on their national market, and the generic medicines applicant is forced either to withdraw the application from one or more countries in order to save the others, or is forced into costly and time consuming arbitration proceedings. In other cases, harmonized generic medicines authorisations may be achieved by establishing what is known as “horizontal harmony”. But the resulting SPC differences between generic and originator SPCs, known as “vertical disharmony”, is often considered unacceptable to national authorities. As a result, the generic medicine will not be included in lists allowing substitution or reimbursement in those countries, which in turn limits, or even blocks, sales of the lower-priced product, denying the potential savings to patients. [7]

2.5.2 Contested Applications:
If disagreements between the CMS over the acceptability of an application remain unresolved at a certain point, the issue is automatically referred to the relevant Committee at the EMEA, Committee for Medicinal Products for Human Use (CHMP), for arbitration. The opinion of the CHMP is then communicated to the European Commission for a final decision.

In practice, however, this recourse has not proven very effective and has received only limited use largely due to its cost to the generic medicines company in terms of finance, human resources and, most importantly, the delay to market in other Member States. [7]

2.5.3 Recent Position of Competent Authorities:
The Co-ordination Group for Mutual Recognition and Decentralised Procedures-Human CMD(h) published in November 2006 their position regarding approval of generic medicines products in case of differences in the indications as compared to the reference product.

A deviation in indications (more or fewer) in the generic medicine, not in line with the SPC of the national reference product is not considered per se to be an appropriate reason to refuse licensing to the generic medicine applicant.

In accordance with the art.30.2 of the revised Directive 83/2001, in order to promote harmonisation of medicinal products containing the same active substance, but having disharmonised product information among EU countries, the CMD(h) should propose an annual list of products to be revised. [7]

2.6 Conclusion:
This review article attempts to an insight on the recent regulatory aspects and marketing authorisation procedures in Europe by giving a detailed overview of the centralised procedure, mutual recognition procedure and revised decentralised procedure along with the proper timelines to aid various pharmaceutical applicants to make proper marketing applications and place their products in the European Markets.

In the attempt, author realizes that few loose ends still remain in the regulatory marketing authorisation procedures, and hopes that EMEA would review and resolve them in the coming years.

2.7 Abbreviations:
AIDS-Acquired Immune Deficiency Syndrome
CMS-Concerned Member State
CHMP-Committee for Medicinal Products for Human Use
CPMP-Committee for Proprietary Medicinal Products
EU-European Union
EEA-European Economic Area
EGA-European Generic Medicines Association
EMEA-European Agency for Evaluation of Medicinal Products
MA-Marketing Authorisation
MS-Member State
MRP-Mutual Recognition Procedure
RMS-Reference Member State
SPC-Summary of Product Characteristics

References:


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