

# The licensing of medicines

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An overview of the licensing process as it applies to medicinal products in the UK

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# The licensing of medicines

There are two routes by which a drug may be granted a product licence in the UK:

- via the European Medicines Evaluation Agency (EMA)
- via the Medicines and Healthcare products Regulatory Agency (MHRA).

## The role of the EMA in the licensing process

The EMA was established in 1995 to co-ordinate the processing of European Union (EU) licence applications. The aim was to streamline the licensing process and ensure a homogeneous regulatory policy throughout the EU.

The EMA is part of the EU Commission whose aim is *“to promote the protection of human health and consumers of medicinal products”*. In 2000, the Commission reviewed the role and function of the EMA. The Commission’s recommendations are currently going through the process of agreement by EU Health Ministers and presentation to the EU Parliament for ratification.

The EMA comprises three committees:

- Committee for Proprietary Medicinal Products (CPMP)
- Committee for Veterinary Medicinal Products (CVMP)
- Committee for Orphan Medicinal Products (COMP)

The CPMP is the advisory committee to the EMA for human medicinal products and comprises two delegates from each EU member country. The vast majority of medicinal products now reach the EU market via the EMA. Before 1995, if a company wanted to market in more than one European country they had to make an application to the licensing authority in each individual country. The EU system allows one application to be made resulting in an EU-wide licence.

There are two ways an EU product licence can be obtained, by the centralised system or by the decentralised system (also known as the mutual recognition system).

## The EU centralised system

Since 1995, the centralised system (see figure 1) has been obligatory for biotechnology products. Following review of the EMA, EU health ministers have agreed this system should also now be compulsory for new products for the treatment of AIDS, cancer, neurodegenerative diseases and diabetes. Drugs going via this route will have a longer period of exclusivity (10 years) compared to those going via the decentralised system (8 years).

The process of application via the centralised system involves the pharmaceutical company filing an application with the EMA. This is then passed to the CPMP. Representatives from two member states are selected to consider the application, one of which is chosen by the pharmaceutical company. These are known as the ‘rapporteur’ and ‘co-rapporteur’ member states. Their assessments form the basis for the final approval by the CPMP. Following assessment the CPMP gives an ‘opinion’ on the application, which, in turn, is considered by the EU Commission who are the licensing authority.

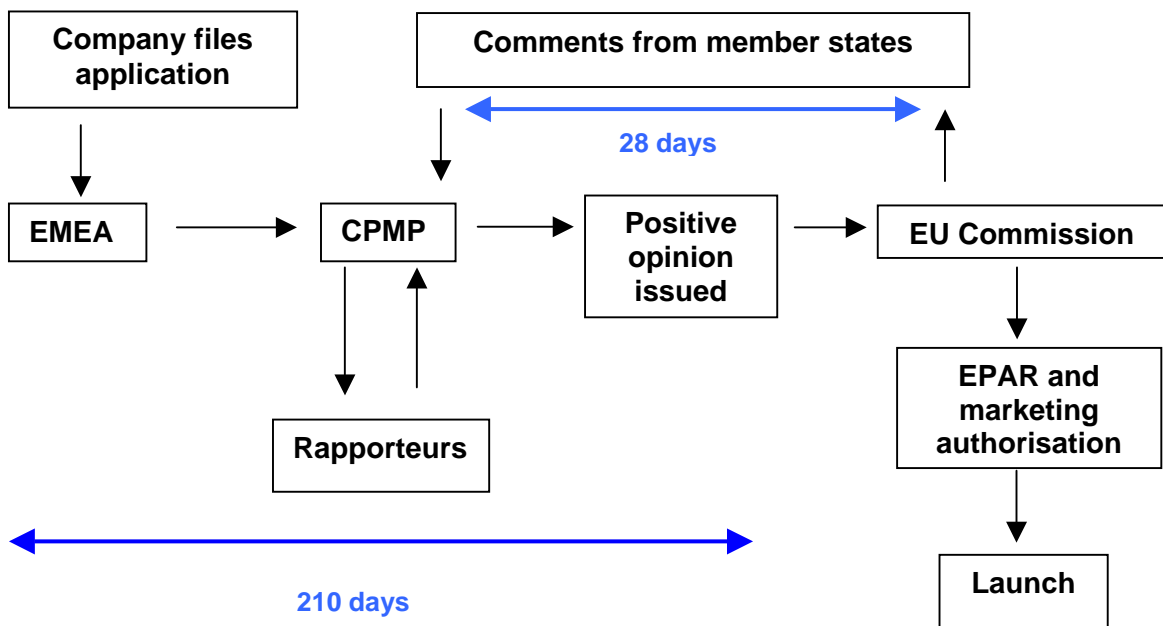
The CPMP work to a strict timetable laid down in EU law. An ‘opinion’ (positive or negative) has to be issued within 210 days of receipt of the application, although the company may stop the procedure at any time. A preliminary review is undertaken early on in the process. The result is revealed to the company who may decide to continue with or withdraw the application. Under new proposals it is hoped that the advice given to companies prior to application can be improved to tackle the problem of premature applications and application withdrawals. Summaries of the CPMP opinion are published on the EMA website. Although 210 days is the maximum time allowed for issuing an opinion, the average time actually taken is 180 days.

If the opinion is negative the company must answer questions raised by the CPMP before the application can be progressed. If a positive opinion is issued, the EU Commission requests comments from other member states, which have 28 days to

respond. Any objections to the rapporteur's decision are considered by the CPMP, which then makes a recommendation for or against an EU-wide licence. If a licence is recommended a European Public Assessment Report (EPAR) is produced and marketing authorisation issued. The EPAR reflects the conclusion reached by the CPMP and is published on the EMEA website after

removal of commercially confidential information. It also contains the Summary of Product Characteristics and supplementary information considered by the CPMP. The company is then able to market in any EU country. However, the company may decide not to launch in a particular country for commercial reasons or because the market is not considered suitable.

**Figure 1. The European Union centralised system**



***Decentralised (or mutual recognition) system***

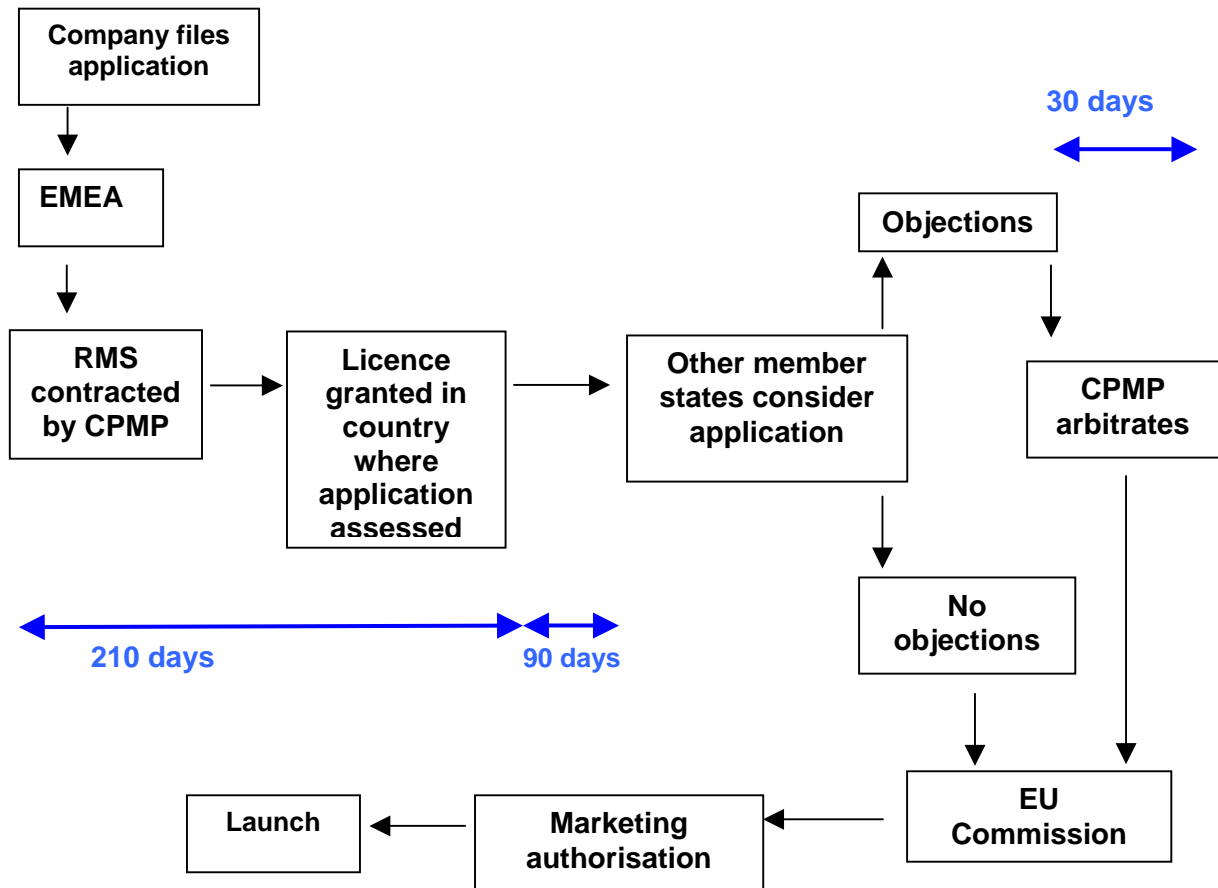
Under this system the CPMP co-ordinates the system, but does not take any part in the decision-making process unless there is disagreement between member states (see figure 2).

Following receipt of an application the CPMP contracts one member state of the EU to assess the application. The contracted state is termed the reference member state (RMS). In the UK, the agency that would evaluate the application under both systems is the Medicines and Healthcare products Regulatory Agency (MHRA). The RMS is contracted to grant a licence within a maximum of 210 days. The company applying for a licence has the right

to choose which RMS will evaluate their product.

Once the RMS has approved the product other member states have 90 days to 'mutually recognise' the approval. The other countries may raise objections if there are concerns about safety, or major scientific or public health issues. However, cynics believe some countries object on purely political grounds. In this situation the CPMP acts as arbitrator and currently has 30 days to make a decision. It is proposed that this period should be reduced to 15 days. The advice of the CPMP to the EU Commission is binding and each country then issues its own marketing authorisation.

**Figure 2. The European Union decentralised (or mutual recognition) system**



Once a product has a marketing authorisation it is then 'licensed', 'registered' or 'approved'. All these terms have the same meaning. The company is then free to approach individual governments to market the product. It is at this point that other factors come into play, loosely termed 'the fourth hurdle'. These may include pricing negotiations, which can significantly delay launch. The median time from marketing authorisation to launch in the UK is 20 days. Under the EMEA review it is proposed that if a product has not been launched within three years of approval, the marketing authorisation will cease to be valid.

The problem with this route is that it leads to different outcomes in different countries. Pharmaceutical companies believe that the mutual recognition procedure can, in some cases, offer a greater chance of approval as they simply avoid filing applications in member states where approval is doubtful.

Historically, the UK licensing system has been one of the fastest in the world closely followed by the Swedish licensing system. Therefore, it is no surprise that the majority of EU applications go through the UK or Swedish systems. Whilst the aim of the review of the EU process is to speed up applications, the licensing authority in the US (Food and Drug Administration) has slowed down their approval system. There is speculation this is related to removal of several newly approved drugs from the market in recent years because of safety concerns. Although there are more new products in development than ever, there are fewer getting to the phase III study and registration stage.

Under the new proposals it is likely that licences will be reviewed after five years and that licence renewal will be done on the basis of a comparative reassessment of the product's risk benefit balance.

## Orphan drugs

Since 2000, the COMP has considered applications for those drugs that have no financial benefit to pharmaceutical companies because the target population is too small. These are known as orphan drugs. Orphan drug status is granted to products that treat life-threatening or severely debilitating diseases affecting less than 5 in 10,000 residents in the EU and for which no satisfactory alternative is available. Companies developing products granted orphan drug status are eligible for incentives to support research and development. The period of market exclusivity for drugs with orphan drug status is 10 years in the EU and 7 years in the US.

## The role of the MHRA in the licensing process

The Medicines and Healthcare products Regulatory Agency (MHRA) is the regulatory authority for medicines in the UK. It was formed in 2003 from the merger of the Medicines Control Agency (MCA) and the Medical Devices Agency (MDA). Prior to the establishment of the EMEA in 1995, the MCA was the only route by which medicines could obtain a product licence in the UK. The role of the MCA/MHRA has changed substantially since 1995. A substantial part of the MHRA's work is now to support the European process. However, whether the MHRA receives an application for a product licence as the sole agency or as part of the

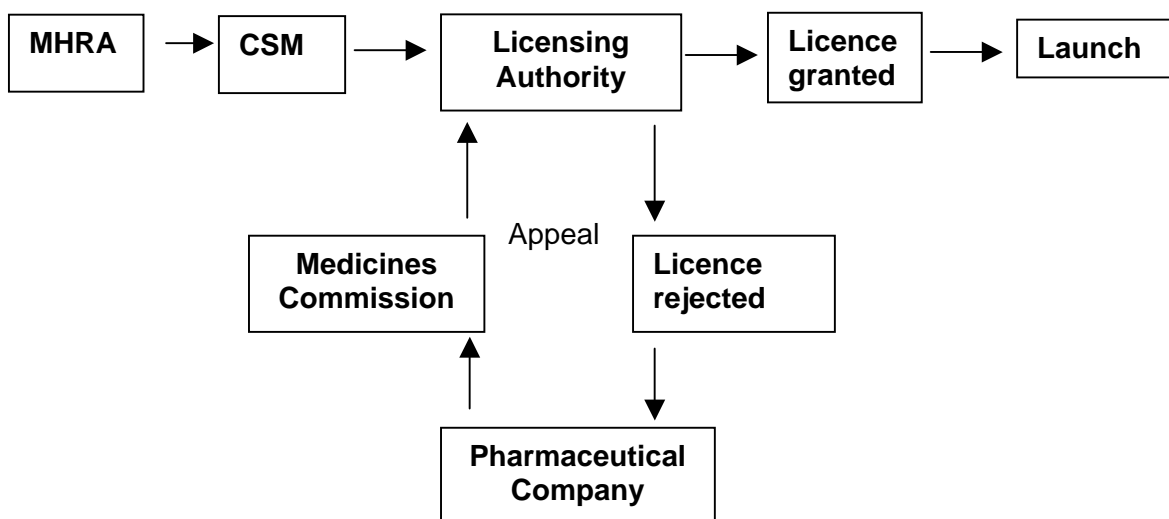
European system, the processes involved are essentially the same (see figure 3).

When applying for a licence the pharmaceutical company will submit a file to the MHRA, or the file will be received via the EMEA if the application is via the EU. The Committee on Safety of Medicines (CSM) within the MHRA will review the application and produce an independent assessment. The CSM is the advisory committee in the UK that can be considered equivalent to the CPMP in the EU. The CSM will either recommend a licence be granted, accept the application subject to modifications or reject the application with reasons.

If the CSM recommends to the licensing authority that a licence is granted and the licencing authority believes the medicine is of acceptable quality, is safe and effective and can give overall benefit to patients, a licence will be granted. The Medicines Act specifically excludes from the licensing criteria any consideration of comparative efficacy. If no additional information is requested the time from the application to the granting of a licence takes around 70 working days.

Should the application be rejected, the company can appeal to the Medicines Commission - an advisory body established under the Medicines Act. It comprises a group of experts, appointed by health ministers, who reassess the data and advise the Licensing Authority.

Figure 3. The UK licensing process



## Glossary of terminology used in licensing processes

<p><b>Accelerated approval or review</b> (also known as 'fast track') NB. This is not the same as priority review.</p>	<p>If a product has been granted accelerated approval status the licence processing time is approximately halved. In this situation data on "surrogate" endpoints may be used as a basis for approval i.e. the effect on a marker of the disease, rather than an actual effect on survival or illness. The EU system grants accelerated approval based on the seriousness of the disease, the absence or insufficiency of an appropriate alternative, and anticipation of high therapeutic benefit. Approval is often given on condition that actual clinical benefit is subsequently assessed. If a product has been assigned accelerated status, an opinion may be granted within 120 days of application, instead of the usual 210 days. Following approval the company will be required to submit further data specifically requested by the licensing authority that may subsequently re-assess the application.</p>
<p><b>Advisory committee</b></p>	<p>This is the Committee for Proprietary Medicinal Products (CPMP) in the EU, Committee on Safety of Medicines (CSM) in the UK, or a specialist subcommittee of the Food and Drug Administration (FDA) in the US. These committees advise on the suitability of a product for licensing in their relevant markets. Licensing authorities are not bound by committees' recommendations, but generally follow their advice.</p>
<p><b>Approved</b></p>	<p>An 'approved' product has been granted a product licence or 'marketing authorisation'. In the EU each country will issue individual marketing authorisations following price negotiations. However, approval does not mean it is available for use. A product has to be 'launched' before it can be prescribed. The company may decide to launch the product in a particular country within a few days of approval, several years later, or maybe not at all.</p>
<p><b>Centralised system</b></p>	<p>One of the two systems whereby a product is licensed in the EU, the other being the decentralised system (see page 2).</p>
<p><b>COMP</b></p>	<p>Committee for Orphan Medicinal Products, one of the advisory committees of the EMEA. (see page 5).</p>
<p><b>CPMP</b></p>	<p>Committee for Proprietary Medicinal Products, one of the advisory committees of the EMEA.</p>
<p><b>CSM</b></p>	<p>Committee on Safety of Medicines, the committee within the MRHA that advises on the suitability of a product for licensing in the UK.</p>
<p><b>Decentralised system</b></p>	<p>This is the alternative to the centralised system in the EU and is also known as the mutual recognition system (see page 3).</p>
<p><b>EMA</b></p>	<p>European Medicines Evaluation Agency <a href="http://www.emea.eu.int">www.emea.eu.int</a>. The EU regulatory agency that reports to the EU Commission.</p>
<p><b>EPAR</b></p>	<p>The European Public Assessment Report (EPAR) reflects the conclusion reached by the CPMP in the centralised process. It is a summary of the grounds for the positive opinion in favour of granting a marketing authorisation and is posted on the EMEA website after deletion of commercially confidential information. It contains details of clinical trials, the Summary of Product Characteristics and, sometimes, comments made by the advisory committee members.</p>
<p><b>EU Commission</b></p>	<p>The EU licensing authority responsible for granting product licences.</p>
<p><b>Exceptional circumstances</b></p>	<p>If a licence is granted in the EU system "under exceptional circumstances" the company are under specific obligations defined by the licensing authority that may include conducting further studies and notification of adverse reactions. This happens where comprehensive data are not available for objective and verifiable reasons such as the indications are very rare, in the present state of scientific knowledge comprehensive information cannot be provided, or it would be unethical to collect such information. The licence will be granted on the following conditions:</p> <ul style="list-style-type: none"> <li>• An identified programme of studies is completed within a time period specified by the licensing authority. The results will form the basis of a reassessment of the risk/benefit profile.</li> <li>• The product may only be administered under strict medical supervision by an authorised person.</li> <li>• The product information states that data available are limited and inadequate in certain aspects.</li> </ul>
<p><b>Expanded access</b></p>	<p>A mechanism that allows investigational drugs to be used in "expanded access" protocols prior to licence application. The intent is to learn more about the drugs, especially their safety, and provide treatment for people with immediately life-threatening or otherwise serious diseases for which there are few alternatives.</p>

<b>Glossary of terminology used in licensing processes</b>	
<b>Fast track</b>	See accelerated approval.
<b>Filed</b>	If a product has been filed it means the licensing authorities have accepted an application for a product licence. In relation to the EU procedure, the maximum time frame from accepting an application to issuing an opinion is 210 days, excluding clock stops when the company provides additional information.
<b>Launched</b>	A product is marketed in a particular country. See also 'approved'.
<b>Licensed</b>	See approved.
<b>Marketing authorisation</b>	The authority given by the licensing authority to the company to allow marketing of the product. See also 'approved'.
<b>Member state</b>	EU member countries taking part in the EU licensing process for medicines.
<b>MHRA</b>	Medicines and Healthcare products Regulatory Agency, the regulatory agency in the UK. <a href="http://www.mca.gov.uk">www.mca.gov.uk</a>
<b>Mutual recognition system</b>	See decentralised system.
<b>Opinion</b>	In the EU, if the product is going through the centralised route, an opinion is issued by the CPMP as to the suitability of the product for licensing.
<b>Orphan drug</b>	See page 5.
<b>Pivotal phase III studies</b>	Pivotal PIII studies are those that are designed to be pivotal to the licence submission. Interim results will guide the future development of the product. If they are poor, the company may decide to await full results, suspend development, or redesign studies. The results of these are crucial for licence applications and will dictate the further development of a product.
<b>Pre-registration</b>	This means the same as 'filed', an application has been filed and accepted by the regulatory agency.
<b>Priority review</b>	Products are eligible for priority review if they provide a significant improvement compared to marketed products in the treatment, diagnosis, or prevention of a disease. This is not the same as fast track status.
<b>Rapporteur</b>	Via the centralised EU system, two member states are selected to consider the application on behalf of the CPMP. These are known as the 'rapporteur' and 'co-rapporteur' member states.
<b>Registered</b>	See approved.
<b>Reference member state (RMS)</b>	An EU country that will look at the licensing of a product in the decentralised (or mutual system) of the EU.

### **Bibliography:**

1. Garattini S, Bertele V. Adjusting Europe's drug evaluation to public health needs. *Lancet* 2001; 358; 64-67
2. Fewer new products force EMEA budget cut. *Chemist and Druggist* 12 October 2002
3. Anon. Commission amends review proposals. *Scrip* 2003; 2843/44: 3
4. Bouayad S. The European Agency for the Evaluation of Medicinal Products (EMEA). *Eur. J. Hosp. Pharm.* February 2003; 9(2): 38
5. Anon. EU review proposals published. *Scrip* 2003; 2845: 5
6. Anon. Ministers agree on EU review proposals. *Scrip* 2003; 2855: 5