Pharmaceuticals Export Promotion Council of India

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

REGULATORY & MARKET PROFILE OF BELGIUM

DEMOGRAPHY

SL. No	Parameter	Description

1	Region	Europe
2	Country	Belgium
3	Capital	Brussels
4	Population	11,570,762 (July 2018 est.)
5	Population growth rate (%)	0.67% (2018 est.)
6	GDP (purchasing power parity)	$ 529.92 Billion (2017 est.)
7	GDP - real growth rate (%)	1.7% (2017 est.)
8	GDP - per capita (PPP)	$ 46,600 (2017 est.)
9	Epidemiology	Cancer, ischemic heart diseases, respiratory and digestive system conditions Psychosomatic disorders
10	Population below poverty line	15.12%(As per 2013, No update)
11	Age structure (%)	0-14 years: 17.2%
		15-24 years11.25%
		25-54 years: 39.82%
		55-64 years: 12.96%
		65 years and over: 18.78%
Source: CIA World Fact Book updated to July 2018		

MARKET REPORT

Introduction:

Although the policymaking environment is unlikely to see an immediate improvement to burdensome pricing and reimbursement regulation, key improvements - with respect to healthcare access, investment, and digital transformation - support the positive growth trajectory for Belgium's health and pharmaceutical sector.

Market size was of $ 6.75 billion in 2017 and is expected to grow by 7.2% and reach $ 7.23 billion in 2018.

Latest Updates

- In August 2018, Janssen announced the renewal of an innovation charter with Ghent University and Ghent University Hospital, as part of an initiative to share more knowledge and expertise, stimulate scientific talent, and reduce the time required for innovations to reach patients.
- In September 2018, the Federal Agency for Medicines and Health Products (FAMHP) announced that the good manufacturing practices guide (GMP) will be available in French and Dutch on the FAMHP website for the first time.

Strengths

- One of the highest per capita spending rates on drugs in the world, supported by high consumption levels of patented medicines.
- A significant base for biopharmaceutical companies, such as GlaxoSmithKline Biologicals. Favourable geographic location, skilled workforce and high quality of life.
- An international pharmaceutical distribution centre.
- Modernisation of drug registration, pricing and reimbursement processes, leading to faster processing times.
- Continued commitment to cutting drug prices is boosting pharmaceutical consumption
- Doctors obliged to prescribe cheaper products due to quotas.

Weaknesses

- Generic substitution is not permitted, although if a doctor prescribes a medicine by the international non-proprietary name (INN), the pharmacist may dispense either a branded product or a generic substitute.
- Political discord concerning budgetary savings in the healthcare sector.
- Mature pharmaceutical market, with a relatively low annual growth potential.
- The OTC medicines sector is underdeveloped due to restrictions on the sale of non-prescription items.

Opportunities

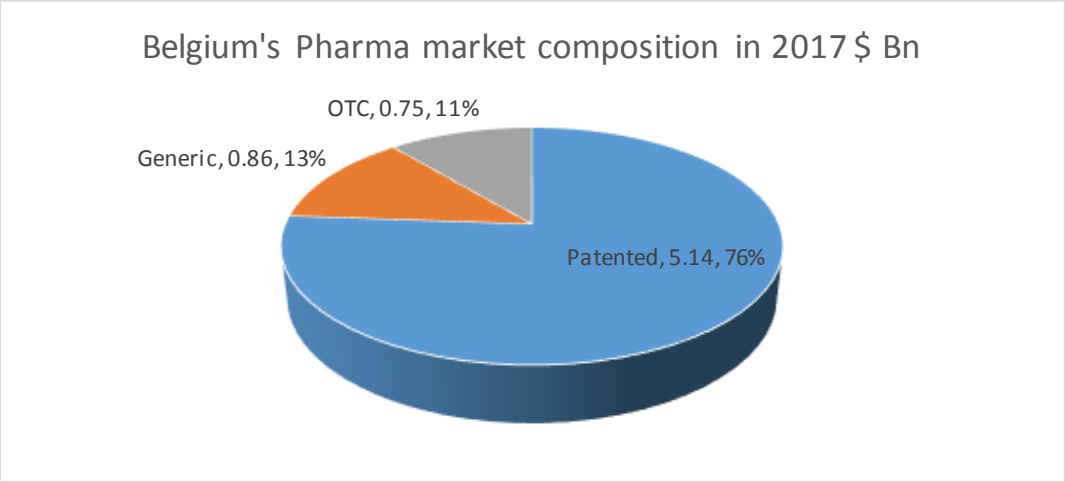
- High growth potential for the generic drug market as the government increases its focus on cost containment.

- Ageing population likely to lead to growing demand for pharmaceuticals for chronic non-communicable conditions, such as Alzheimer's disease and cancer.
- The government's move to amend taxation legislation to support the biotechnology industry in the country.
- Proactive pursuit of international trading partners in Asia and the Middle East.

Market

Belgium's pharmaceutical market is one of the largest in the region and is equivalent to 1.4% of the country's GDP. The market is dominated by the sale of high-value patented prescription medicines. Prescription drugs account for 88.9% of sales with the remaining 11.2% made up by OTC sales.

Percapita spending in 2017 was $ 590.



The leading local companies in terms of market capitalisation are UCB and Omega Pharma. A large number of foreign pharmaceutical firms are also already present in the Belgian market, including Pfizer and GlaxoSmithKline.

The Belgian pharmaceutical market continues to show steady growth as its health sectors enter a phase of rapid technological development to improve healthcare streamlining. Already underpinned by an ageing population, the digital transformation is likely to further support pharmaceutical consumption, as the move to electronic systems increases the rate and efficiency of dispensing prescriptions. At the same time, critical e-health investments will also advance Belgium's position as one of the leading global centres for clinical research and pharmaceutical innovation.

Being a major exporter of chemicals and medicines (second to only to Germany in the EU), its well-developed network of education and research institutions has ensured Belgium's pharmaceutical sector remains at the forefront of innovation and an important European destination for pharmaceutical investment.

The market is forecast to rise to USD7.96bn by 2022, experiencing a compound annual growth rate (CAGR) of 3.4%.

Alongside health regulators across Western Europe, the National Institute of Health and Disability Insurance (INAMI) has implemented a number of cost-cutting measures, including the extension of reference pricing systems to curb reimbursement spending and the introduction of incentives to encourage prescription of generic drugs.

Slowly expanding the prescription of generic medicine will restrain the pace of overall pharmaceutical market growth. As one of the world leaders in the pharmaceutical industry, Belgium plays an instrumental role on the international scene in terms of access to treatment, as evidenced by its negotiation with pharmaceutical companies to increase access to, and lower prices for, innovative medicines in the Netherlands, Luxembourg and Austria.

In September 2017, a forum to promote economic ties between Vietnam, Belgium and other EU states was held in Brussels, during which the Vietnamese government encouraged firms to ratify the Vietnam-EU Free Trade Agreement (EVFTA), something that is expected to create opportunities in pharmaceutical trade for both sides. Lacking from recent initiatives has been an effective programme of financial incentives to encourage prescription of cheaper biosimilar alternatives to popular biologics.

Generic Market

The uptake of generic drugs following patent expiry is set to become swifter. This trend will reduce costs for governments, out-of-pocket payers and insurance companies, which is increasingly important as developed states reform their healthcare systems over the medium term. Key obstacles include prescribers' brand loyalty, pay-to-delay deals, the near-universal unpopularity of commodity generics and a lack of perfect competition in the pharmaceutical sector.

Belgium, among the lowest in the region by value, will continue to lag markets such as Germany due to strong patient and prescriber bias towards branded drugs along with a lack of price transparency throughout the pharmaceutical value chain. Generic medicine sales were valued at USD857mn in 2017. Forecasts say generic drug sales is to increase by 8.0% to USD925mn, making up 12.8% of sales (14.4% of prescriptions), by 2018. By 2022, it is forecasted that the market would grow at a CAGR of 4.2% and reach USD1.05bn and to account for 13.2% of sales (14.9% of prescriptions).

Although generic substitution is not permitted in Belgium, if physicians prescribe by International Non-proprietary Name (INN), the pharmacist is obliged to deliver least priced pharmaceutical if one exists (in the form of either a generic pharmaceutical or an original pharmaceutical with a price equal to the reimbursement price). Until now, doctors and dentists have been obliged to prescribe 50% of the least priced drugs on the market (often generics), with the quota set to increase to 60% from 2017, which will be positive for the healthcare budget and certain patients.

Due to implementation of price controls , as of April 2018, Belgium is in the midst of a drugs supply shortage, with the Association of Belgian Pharmacists (APB) releasing a list of nearly 400 medicines unavailable on the market. The Federal Agency for Medicines and Health Products (FAMHP) is working to find solutions to the problem caused by pharmaceutical company cost-cutting and interruptions to the primary supply chain. To tackle the problem, Health Minister Maggie de Block has suggested pharmacists may be given special powers to offer alternatives to the patients without them

having to return to a doctor, which could result in a temporary, but sizeable boost to the generics market.

Pharma Trade

Despite challenges in the domestic market, Belgium maintains a strong pharmaceutical industry, as evidenced by the positive pharmaceutical trade balance.

In 2017, pharmaceutical imports were valued at USD32.87bn against pharmaceutical exports of USD41.15bn. For 2018, pharmaceutical imports are expected to rise by 12.1% to USD36.84, against pharmaceutical exports of USD45.49bn, growing by 10.5% . By 2022, pharmaceutical exports are forecast to increase to USD61.70n with sector imports rising to USD50.84bn, resulting in a trade balance of USD10.86bn.

According to UN Comtrade, the leading countries of import origin are Germany, Ireland and France. Belgium's leading pharmaceutical export partners are Germany, the US and France, followed by the UK, Italy and Spain.

In August 2016, the prime minister of Flanders proposed a radical North Sea Union linking Britain to a cluster of regional states to cushion the Brexit shock, a sign that European leaders are starting to look for creative ways to heal the referendum rift.

Many drug makers use Belgium as an international distribution centre, meaning that import and export trade in pharmaceutical products far exceeds the value of the domestic market. Exports are expected to follow a steady upward trend as Belgium remains a key European distribution site for multinationals.

Epidemiology

Chronic diseases, such as malignant neoplasms and neuropsychiatric conditions, place a high burden on Belgium's healthcare services. In fact, in 2017, DALYs lost to non-communicable diseases accounted for 95% of the total disease burden.

In terms of mortality, diseases of the circulatory system (and ischaemic heart disease in particular) account for over one-third of total deaths. The second leading cause of death is cancer (prostate and lung in men, and breast and colon in women), which is responsible for over a quarter of total deaths. Other major causes of death are respiratory and digestive system conditions.Psychosomatic diseases are also on the rise.

Local Industry

Belgium has a favourable geographical location at the heart of the EU and this, combined with its highly skilled workforce and favourable tax regime. Further attractions include a well-developed healthcare system that enjoys high government contributions towards overall costs, a large drug market and high per capita spending on medicines, along with a stringent regulatory climate (which is recognised by the US and in line with the EU legislation), large demand for patented products and a stable and transparent business environment.

The pharmaceutical industry association, Pharma.be, had 130 members in 2016, jointly representing around 84% of people employed by the pharmaceutical industry in the country. Overall, Belgium is a

relatively modest producer of pharmaceutical products, despite being a world leader in the production of vaccines. The majority of indigenous producers are small companies and only a handful of multinationals have made Belgium a key manufacturing site.

Domestically produced pharmaceutical products contribute significantly to Belgium's pharmaceutical exports. About 40% of domestic output - mostly manufactured by small companies - is intended for the local market, with the remainder exported. One of the strongest local pharmaceutical industry sectors is the production of vaccines. As an example, about 90% of GlaxoSmithKline's Belgian output is exported, accounting for about 25% of the country's pharmaceuticals exports.

The leading local companies in terms of market capitalisation are UCB Pharma (USD6.56bn) and Omega Pharma (USD1.25bn). Other smaller local players include Besins, Laboratoires SMD (which focuses on over-the-counter drugs (OTCs) and prescription areas of the respiratory tract, the cardiovascular system, and pain management), Sterop (which also manufactures food supplements) and Sanico.

Statistics:

India's Pharmaceutical exports to BELGIUM $ Million

Category	2015-16	2016-17	2017-18	GR%	contbn%	Contbn to Region
Bulk drugs and drug intermediates	79.89	91.65	76.56	-16.46	31.52	8.50
Drug formulations and biologicals	102.43	130.98	157.69	20.39	64.92	9.76
AYUSH	0.49	0.20	0.18	-11.27	0.07	0.80
Herbal Products	3.84	4.77	6.07	27.14	2.50	5.81
Surgicals	4.97	2.96	2.19	-25.90	0.90	2.11
Vaccines	0.49	0.59	0.19	-67.88	0.08	6.58
Total	192.12	231.16	242.88	5.07	100.00	8.83

Belgium 's Top ten formulation Importing partners $ Million

Rank	Country	2015	2016	2017	Gr%	Share %
1	USA	9890.32	9253.24	7108.76	-23.18	20.89
2	Ireland	5879.84	5813.01	6869.42	18.17	20.18
3	Italy	5774.52	5285.65	4415.20	-16.47	12.97
4	Switzerland	2279.19	2464.28	3364.83	36.54	9.89
5	France	3224.30	3032.00	3070.73	1.28	9.02
6	Germany	2493.85	2376.65	2268.18	-4.56	6.66
7	Netherlands	1418.94	1607.24	1641.79	2.15	4.82
8	Singapore	1529.71	1156.30	856.60	-25.92	2.52
9	United Kingdom	706.00	715.65	791.48	10.60	2.33
10	Canada	677.48	514.12	646.73	25.79	1.90
18	India	109.00	145.10	174.41	20.20	0.51
19	World	36277.05	35014.70	34035.42	-2.80	100.00

Source:UN comtrade

REGISTRATION AND LICENSING REQUIREMENTS

➢	Regulatory Authority	:	**famhp (Federal Agency for Medicines and Health products) / European Medicines Agency (EMA)**
➢	Website of regulatory Authority	:	https://www.famhp.be/en http://www.ema.europa.eu/
➢	Fees for Drug Registration	:	27,089€ for Generic Application in National Procedure
➢	Normal time taken for registration	:	12 - 18 Months
➢	Registration Requirement [Dossier Format]	:	e-CTD
➢	Whether plant inspection is mandatory	:	Yes

EMA Organization:

The European Medicines Agency (EMA) is a decentralised agency of the European Union (EU), located in London and will relocate to Amsterdam. The Agency is responsible for the scientific evaluation, supervision and safety monitoring of medicines in the EU.

EMA protects public and animal health in 28 EU Member States, as well as the countries of the European Economic Area, by ensuring that all medicines available on the EU market are safe, effective and of high quality.

EMAs activities:

Facilitate development and access to medicines

EMA is committed to enabling timely patient access to new medicines, and plays a vital role in supporting medicine development for the benefit of patients. The Agency uses a wide range of regulatory mechanisms to achieve these aims, which are continuously reviewed and improved. They are

- Support for early access;
- Scientific advice and protocol assistance;

- Paediatric procedures;
- Scientific support for advanced-therapy medicines;
- Orphan designation of medicines for rare diseases;
- Scientific guidelines on requirements for the quality, safety and efficacy testing of medicines;
- The Innovation Task Force, a forum for early dialogue with applicants.

EMA also plays a role in supporting research and innovation in the pharmaceutical sector, and promotes innovation and development of new medicines by European micro-, small- and medium sized-enterprises.

Evaluate applications for Marketing Authorisation

EMA's scientific committees provide independent recommendations on medicines for human and veterinary use, based on a comprehensive **scientific evaluation of data**.

The Agency's evaluations of marketing-authorisation applications submitted through the **centralised procedure** provide the basis for the authorisation of medicines in Europe.

They also underpin important decisions about medicines marketed in Europe, referred to EMA through referral procedures. EMA coordinates inspections in connection with the assessment of marketing-authorisation applications or matters referred to its committees.

Monitor the safety of medicines across their lifecycle

EMA continuously monitors and supervises the safety of medicines that have been authorised in the EU, to ensure that their benefits outweigh their risks. The Agency works by:

- Developing guidelines and setting standards;
- Coordinating the monitoring of pharmaceutical companies' compliance with their pharmacovigilance obligations;
- Contributing to international pharmacovigilance activities with authorities outside the EU;
- Informing the public on the safety of medicines and cooperating with external parties, in particular representatives of patients and healthcare professionals.

Provide information to healthcare professionals and patients

The Agency publishes clear and impartial information about medicines and their approved uses. This includes public versions of scientific assessment reports and summaries written in lay language.

Federal Agency for Medicines and Health Products (FAMHP)

About the FAMHP

Federal Agency for Medicines and Health Products, famhp (former Directorate-General for Medicinal Products of the FPS Public Health) was created on 01/01/2007 works under Minister of Social Affairs and Public Health.

Role:

In the interest of public health the FAMHP ensures the quality, safety and efficacy of medicines and health products in clinical development and on the market.

The FAMHP ensures, from development to use, the quality, safety and efficacy of medicines for human and veterinary use (including homeopathic medicines, herbal medicines, pharmacy made and officinal preparations) and also medical devices and accessories, and raw materials for the preparation and production of medicines.

From collection touse, the FAHMP ensures the quality, safety and efficacy of all the operations involving with blood, cells and tissues.

Fields of competency or activities:

- In terms of ***research and development (R&D)*** the FAMHP evaluates, approves, follows and controls the requests for clinical trials for medicines and health products. It also give scientific advice.
- In terms of ***registration or marketing authorisation of medicines***, the FAMHP is in charge of evaluating new requests for registration or marketing authorisation of a medicine or of requests to change existing registrations or marketing authorisations.
- In terms of ***vigilance*** the FAMHP supervises the adverse effects due to the use of medicines or health products by collecting information. Information is gathered and evaluated and, if necessary, measures are taken.
- In terms of ***production and distribution*** the FAMHP grants authorisations and checks that medicines and health products are conform current regulations concerning manufacture, distribution, delivery, imports and exports. It also controls pharmacists' activities and combats illegal practices.
- In terms of ***proper use*** the FAMHP sees to it that patients have relevant information so that medicines and health products are used rationally and safely. It also controls advertising for medicines and health products.

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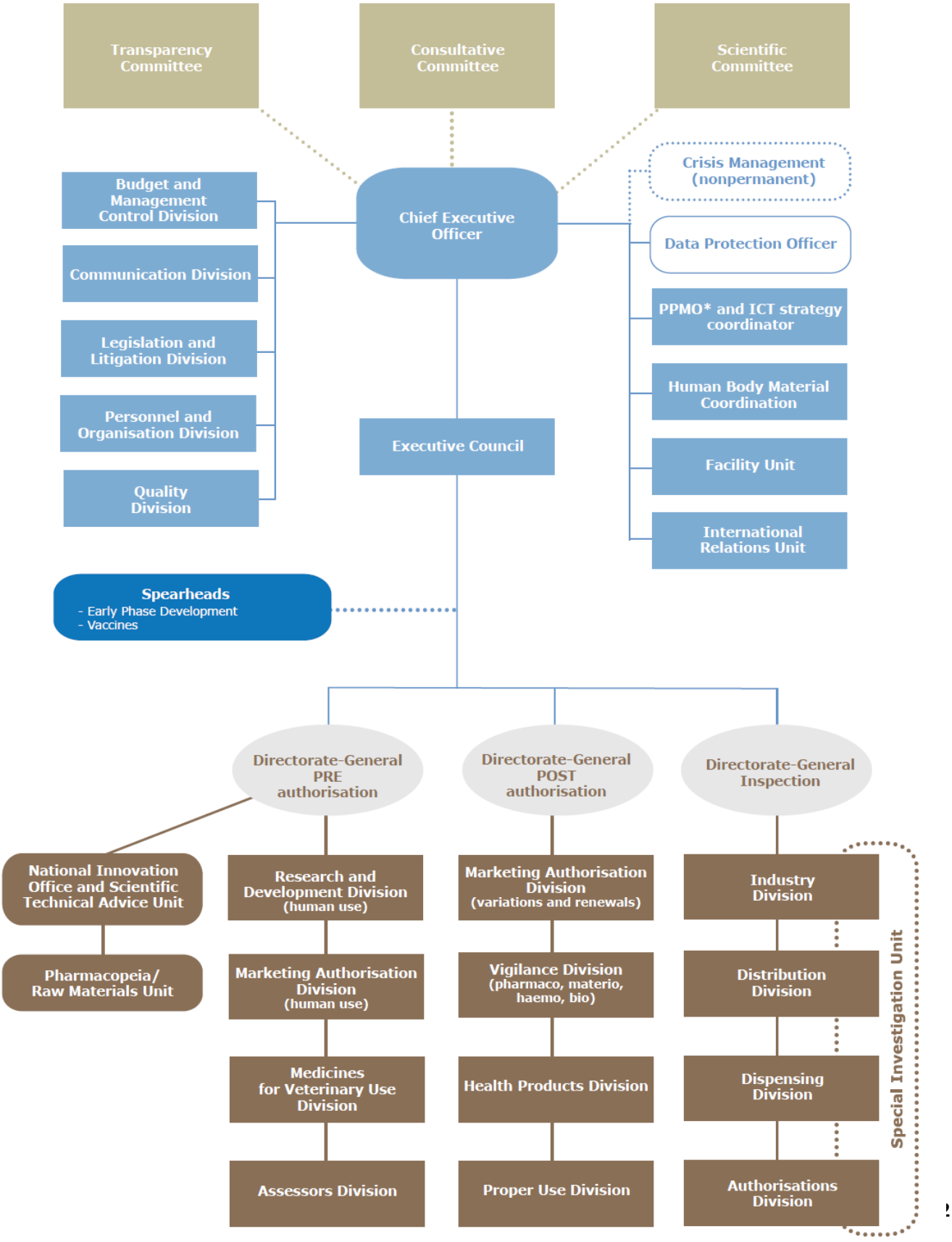
Organisation Chart of the FAMHP



AUTHORISATION OF MEDICINES

All medicines must be authorised before they can be marketed and made available to patients. In the EU, there are two main routes for authorising medicines: **a centralised route** and **a national route**. The data requirements and standards governing the authorisation of medicines are the same in the EU, irrespective of the authorisation route.

Centralised authorisation procedure

Under the centralised authorisation procedure, pharmaceutical companies submit a single marketing authorisation application to EMA.

This allows the marketing-authorisation holder to market the medicine and make it available to patients and healthcare professionals throughout the EU on the basis of a single marketing authorisation.

EMA's Committee for Medicinal products for Human Use (CHMP) or Committee for Medicinal products for Veterinary Use (CVMP) carry out a scientific assessment of the application and give a recommendation on whether the medicine should be marketed or not.

Each European Member State has a representative in the CHMP and an alternate. The members of the CHMP are acting in their personal capacity. They act as intermediaries between European and national systems. The CHMP, two rapporteurs, following the product during its entire life cycle, are appointed for each drug .If new request, the CHMP maximum of 210 days to reach a final evaluation. This period can be interrupted to allow the firm to answer questions. There is also the possibility for a firm to give oral explanations on the submitted file. The CHMP final evaluation, the "Opinion", is sent to the European Commission for final decision-making. In case of positive evaluation, the Summary of Product Characteristics (SPC) and the package leaflet are established. A European Public Assessment Report (EPAR: European Public Assessment Report) is made in which any positive or negative opinion is justified. The EPAR (link is external) is published on the EMA website.

After a positive decision, the applicant receives European authorization on the market (AMM), which carries a number that is valid in every Member State of the EU and EEA.

Scope of the centralised authorisation procedure

The centralized procedure is **compulsory** for:

- Human medicines containing a new active substance to treat:
  - HIV or 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.

Steps involved in obtaining an EU marketing authorisation

Submission of eligibility request

18 to 7 months before submission of marketing authorisation application(MAA)
To find out whether a product can be evaluated under the centralized procedure, applicants should always submit an **eligibility request** using the specific form and accompanied by a justification

Notification of intention to submit an application

7 months before submission of MAA
Applicants should consider the date of submission carefully, referring to the published submission dates and the guidance below: Best practice guide on measures improving predictability of submissions/responses and adherence to communicated submission/responses deadlines To notify the Agency of the intended submission date, they should email the pre-submission request form (intent to submit MA) to pa-bus@ema.europa.eu. The selected scope of request should be: 'Centralized Procedure – Intent to submit a MAA'

Appointment of rapporteurs

7 months before submission of MAA
The Committee for Medicinal Products for Human Use (CHMP) and the Pharmacovigilance Risk Assessment Committee (PRAC) appoints (co-)rapporteurs to conduct the scientific assessment. For advanced therapy medicinal products, (co-)rapporteurs are also appointed from members of the Committee for Advanced Therapies (CAT), who will lead the assessment.

Pre-submission meetings

6 to 7 months before submission of MAA
Pre-submission meetings are the best opportunity for applicants to obtain procedural and regulatory advice from the Agency:

Marketing authorisation application pre-submission meeting request form

Successful pre-submission meetings along with the information in the guidance should enable applicants to submit applications in line with legal and regulatory requirements. This speeds up the validation process.

Re-confirmation of communicated submission date

2-3 months before submission of MAA

Applicants should re-confirm the submission date initially communicated to EMA, or inform EMA of any delays or cancellations, following the guidance below:
Best practice guide on measures improving predictability of submissions/responses and adherence to communicated submission/responses deadlines

If the planned submission date is changed, applicants must inform EMA by re-sending the completed pre-submission request form to pa-bus@ema.europa.eu, selecting 'notification of change' as the scope of the request and stating the new intended submission date in the corresponding field.

Holding successful pre-submission meetings and following this guidance should enable applicants to submit applications in line with legal and regulatory requirements, speeding up the validation process.

Submission and validation of the application

Applicants should use the electronic common technical document (eCTD) format and submit the application through the eSubmission gateway or web client.

If the Agency needs additional information to complete its validation of the application, it will ask the applicant to supply this by a deadline. For more information: check What is eSubmission?

Scientific evaluation

Up to 210 active days of assessment

The CHMP evaluates MAA submitted through the centralised procedure. The PRAC provides input on aspects related to risk management and the CAT on advanced therapy medicines.

CHMP Scientific Opinion

After the evaluation, the CHMP must issue a scientific opinion on whether the medicine may be authorized or not.

EMA sends this opinion to the European Commission, which issues the marketing authorization. The Agency then publishes a summary of the committee's opinion.

European Commission decision

Within 67 days of receipt of CHMP opinion

Commission decisions are published in the Community Register of medicinal products for human use and EMA publishes a European public assessment report (EPAR).

When a new marketing authorisation application is refused, the Agency publishes a refusal EPAR, including a question and answer document and an assessment report.

Please check the pre-authorisation guidance for detailed guidance for submission of applications.

Mutual Recognition procedure & Decentralized Procedure

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

If a company wishes to request marketing authorisation in several EU Member States for a medicine that is outside the scope of the centralised procedure, it may use one of the following routes:

- **The Mutual-Recognition Procedure (MRP)**: Whereby a marketing authorisation granted in one Member State can be recognised in other EU countries;

- **The Decentralised Procedure (DCP)**: whereby a medicine that has not yet been authorised in the EU can be simultaneously authorised in several EU Member States.

Mutual-Recognition Procedure (MRP):

- Under MRP, the assessment and marketing authorisation of one Member State ("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))- 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 pre referral 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.

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.

Belgium to act as Reference Member State (RMS):

If you want Belgium (the FAMHP) to act as RMS for your file introduced via the decentralized procedure, follow the guidelines described in the RMSship AFMPS Strategy and the RMS request document. In the case of a Repeat Use (RUP) procedure, the Request for MRP-RUP document and the corresponding Annex I document must be submitted.

An application for Belgium to act as a reference Member State in the mutual recognition procedure must be served upon submission of the national application. When requesting a MRP following a national authorization, the Request for MRP-RUP document and the corresponding Annex I document must be submitted.

National authorisation procedures

In the national procedure, the MA application is submitted by the applicant to the FAMHP. The Commission for Medicinal Products for Human Use appoints the case evaluators and their report is submitted for opinion to the Committee on Medicinal Products for Human Use.

The scientific body within the FAMHP is the Commission for Medicinal Products for Human Use (CMH). The CMH was created to provide advice on marketing authorization applications, the provision of medicines to patients, as well as scientific issues related to medicines. The Commission decides on the benefit / risk balance of a drug based on three criteria: efficacy, safety and quality of the drug.

After an assessment, the applicant receives the decision of the Minister or his delegate. After a positive evaluation, the applicant receives a national MA (bearing a number).

Royal Decree of 14 December 2006 **(Royal Decree on Medicines for Human and Veterinary Use)**

MA application Dossier Requirements:

The MA application dossier must include all the administrative information and all the scientific documentation necessary to demonstrate the quality, safety and efficacy of the medicinal product. At the request shall be accompanied by the following information and documents, presented on the forms by the FAMHP in accordance with Annex I.

1) The name or style and permanent address or head office and, if not it is not the same person, the manufacturer and the persons involved in the manufacturing process of the finished product, as well as the manufacturing steps in which they take place and the place where they take place;
2) The name of the medicine;
3) The qualitative and quantitative composition of all the substances of the medicinal product, including the mention of the International Non-proprietary Name (INN) of the medicine recommended by the World Health Organization when it exists, or its chemical name;
4) The assessment of the potential risks that the medicine might pose to the environment. This impact is studied and, on a case-by-case basis, specific provisions to limit it are envisaged;
5) The description of the manufacturing method;
6) Therapeutic indications, contraindications and adverse effects;
7) The dosage, pharmaceutical form, mode and route of administration and presumed duration of stability;

(8) Explanations of the precautionary and safety measures to be taken when storing the medicinal product, its administration to the patient and the disposal of waste, as well as an indication of the potential risks that the medicinal product might pose to the environment ;

9) A description of the control methods used by the manufacturer and by the parties involved in the manufacturing process;

10) Test results:

- Pharmaceutical (physico-chemical, biological or microbiological) tests,

- Pre-clinical (toxicological and pharmacological),

- Clinics;

(11) A detailed description of the pharmacovigilance system and, where appropriate, the risk management program that the applicant will put in place;

12) A declaration that clinical trials carried out outside the European Union meet the ethical requirements of the law of 7 May 2004 on human experimentation or Directive 2001/20 / EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the application of good clinical practice in the conduct of clinical trials of medicinal products for human use;

(13) A draft summary of product characteristics (SPC), a model of the outer packaging and primary packaging of the medicinal product

14) The following documentation:

- If the manufacturer and those involved in the manufacturing process are established in a Member State: a document showing that the manufacturer and those involved in the manufacturing process are authorized in their country to produce the form pharmaceutical product concerned;

- If the manufacturer and those involved in the manufacturing process are established in a country which is not a Member State but which has concluded a mutual recognition agreement with the European Community on the principles and guidelines of good manufacturing practice medicinal products: a certificate or equivalent document from the national competent authority stating that they are authorized to manufacture the pharmaceutical form of the medicinal product concerned and certifying that the manufacture of the medicinal product concerned is carried out in accordance with the principles and guidelines of good manufacturing practice medicines provided for under Community law;

- In other cases: a declaration from a competent inspection service of a Member State establishing that an authorization to manufacture the pharmaceutical form of the medicinal product concerned has been granted and certifying that the manufacture of the medicinal product concerned is carried out in accordance with Good Manufacturing Practices rules for medicines recommended by the World Health Organization (GMP declaration);

15) A copy of any marketing authorization obtained for the medicinal product in another Member State or in a third country, together with the list of Member States where the marketing authorization application submitted in accordance with the aforementioned Directive 2001/83 / EC is under consideration ; a copy of the SPC proposed by the applicant or approved by the competent authority of that Member State; a copy of the leaflet proposed by the applicant; the details of any decision to refuse a marketing authorization, taken in the Community or in a third country, and the reasons for that decision;

(16) Proof that the applicant has a qualified person responsible for pharmacovigilance, and the means necessary to notify any suspected adverse reaction occurring either in the Community, in a third country.

This information must be updated regularly.

New applications for marketing authorization (MA) for medicinal products for human use are preferably submitted via the Common European Submission Platform (CESP). For practical information, please consult the document Electronic Submission via the CEPA

If you do not use CEPA, send your electronic file by mail or courier to:

FAMHP
DG PRE authorization
Victor Horta Square 40/40
1060 BRUSSELS
Belgium

Once your file is received by the FAMHP, an identification number (ID) is assigned to him. By means of automatic emails, you are kept informed of the process your application within the FAMHP.

Read the National Guideline on eSubmission carefully before submission of your file.

Common Technical Document:

An application for authorization to place a medicinal product for human use on the market must be submitted in CTD format. This is described in Annex I of the Royal Decree of 14/12/2006 on medicinal products for human and veterinary use and in the Annex to the European Directive 2001/83 /EC http: //ec.europa .eu / enterprise / pharmaceuticals / eudralex / vol1_ en.htm

The CTD format includes 5 modules that are identical for all EU Member States. The exact structure of the format is described in part 2B of the Eudralex collection, published by the European Commission http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol2_en.htm .

In this volume, you will find references to European and international guidelines on the scientific content of a dossier and a question and answer document on the practical use of this format in the European Union.

Modules 2 to 5 are identical for the European Union, the United States and Japan. More information can be found on the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceutical Human Use (ICH) website: http://www.ich.org

Technical Validation:

Your file is validated to check if all the documents required by the law are in conformity and present. Some points of attention:

- Further information on the legal basis and the guidelines for medicinal products for human use: http://ec.europa.eu/health/documents/eudralex/vol-2/index_en.htm
- The CMDh has published guidelines related to validation: http://www.hma.eu/91.html
- You can also find the requirements regarding the number of copies, the format, the language used, the samples on the CMDh website; http://www.hma.eu/91.html

Naming guidelines for medicines for human use : Before filing,, carefully read the " National Guideline on Naming ". Acceptance of the proposed name will be facilitated if you take into account the anticipated requirements.

Guidelines for how to deliver a drug:

The following documents give you useful information about how to deliver medications.

- Strategy "delivery mode"
- Narcotics used for palliative care: strategy to limit the sizes of the packaging available in pharmacies open to the public.
- FAMHP guideline on the mode of delivery of antidepressants, antipsychotics, hypnotics, sedatives, anxiolytics and antiepileptics (version 6.2).
- OTC switch guideline

Guidelines for labeling a drug:

Read the document Drug Labeling carefully. Approval of your mock-up and labeling can be done more quickly if you take these recommendations into account.

- **If the active substance belongs to narcotics * or psychotropic substances *?**

- * as mentioned in Annexes I, II and / or IV of the Royal Decree on Narcotic and Psychotropic Substances
- A code must be indicated on the outer packaging of medicinal products marketed in Belgium that contain substances listed in Annexes I, II and / or IV.

- You must request this code from the FAMHP's Specially Regulated Substances Cell via narcotics@fagg-afmps.be once the procedure is approved.
- You must attach to this application the Summary of Product Characteristics (RCP), the draft marketing authorization, or AMM light, and the packaging sizes that will be marketed.
- Then you will receive a code per package size, which you must indicate on the outside packaging mock-up.

Documents to be sent to the FAMHP during the administrative closure phase:

➢ **In case you plan to put the medicine immediately on the market:**

All documents must be sent to the FAMHP for administrative closure phase are taken in the Checklist administrative closure

- Delegation of authority - if the MAH is located abroad.
- Declaration of Conformity NP + English Version + Circular Letter 469
- Summary of Product Characteristics (RCP) in French and Dutch (Circular Letter 469).
- Notice in French, Dutch and German (see circular letter 469).
- Packaging project in French, Dutch and German as well as a mock-up (see circular letter 469).

➢ **In case you do NOT plan to put the medicine on the market immediately:**

All documents must be sent to the FAMHP for administrative closure phase are taken in the Checklist administrative closure

- Delegation of authority - if the MAH is located abroad.
- Declaration of Conformity NP + English Version + Circular Letter 469 (CL 469)
- Summary of Product Characteristics (RCP) in French and Dutch (Circular Letter 469).
- Notice in French, Dutch and German (see circular letter 469).
- Packaging project in French, Dutch and German as well as a mock-up (C. L 469).
- Post-approval commitment mock-up
- Post approval commitment distributor

All documents listed in the Checklist administrative closure must be sent at: prelicensing@afmps.be , indicating the number (ID), the DCP / MRP number and the name of the medication.

Belgian requirements on the Blue Box:

These are additional national requirements for text on the package and the Patient Information Leaflet (PIL).

PACKAGE LEAFLET: mention "Antigifcentrum / Center poisons", AMM number (number BE), mode of delivery (delivery status).

LABELING: reimbursement, legal status, identification and authenticity, certain symbols and pictograms for specific medicines.

You will find more information in the following documents:

- http://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/procedural_guidance/Application_for_MA/CMDh_258_2012_Rev14_03_2018_clean_-_corr.pdf
- Labeling of drugs

Parallel import

A medicine marketed in Belgium as well as in another Member State of the European Union may be imported by a firm from that Member State, provided that a certain number of legal requirements are fulfilled.

This explains why a drug with the same name can be distributed by several firms.The phenomenon of parallel importation is part of the European approach to the free movement of goods, and is applicable in all Member States. European legislation does not stipulate that the composition of the imported medicinal product must be 100% identical to the reference medicine. But the qualitative and quantitative composition of active substances must be the same and the imported medicine must have the same therapeutic effect as the reference medicine. Imported medicines are controlled by the Medicines Commission, so the quality, efficacy, safety and monitoring of medicines are guaranteed.

In order to obtain a parallel import authorization, a number of conditions must be fulfilled, which are described in Article 3, § 2 of the Royal Decree of 19 April 2001 relating to the parallel importation of medicines for human use and parallel distribution of medicines for human and veterinary use. The conditions to be met by the parallel import authorization to maintain its validity are described in articles 6 and 7 of the Royal Decree of 19 April 2001 .

The applicant for a parallel import authorization must compile a dossier and submit it to the Federal Agency for Medicines and Health Products, 40 place Victor Horta, Box 40, 1060 Brussels,

The type of request must be specified:

- new authorization
- variation
- renewal

The file consists of: (see Article 4 of the Royal Decree of 19 April 2001)

- a cover letter
- a form " parallel import authorization "
- a copy of the reference drug package insert
- a copy of the instructions for the imported medicine
- a draft package leaflet: this project must correspond to the latest version of the leaflet of the reference medicinal product which must be accompanied, on the first page, by the planned form (NL , FR , D), which, after approval, will form an integral part of the instructions. This will be available in the packaging of each medicine imported in parallel (see release of 16/08/2012).
- a declaration of conformity indicating that the package leaflet of the imported medicinal product is identical to the package leaflet that is attached to the reference medicinal product. This is subject to the fact that the importer makes adaptations with respect to his identity, the identity of the manufacturer and / or other differences that are mentioned in the declaration.
- a sample of the reference medicine
- a sample of the medicine to be imported, in its original packaging
- a sample or model of the medicinal product as it is intended to be placed on the market in Belgium
- a statement that the original condition of the drug has not been altered directly or indirectly
- a contract between the parallel importer and the repackaging manager
- a GMP certificate if the person responsible for packaging is not established in Belgium

Any application for a parallel import authorization is subject to the payment of a **fee, in** accordance with article 13 of the Royal Decree of 19 April 2001.

Section 1 - 1 °: Request for a parallel import authorization (New request: article 4 or article 7 § 2 and § 3: **1951,20 € / authorization)**

Section 2- 1 °: Renewal (Article 7 § 1: **975,61 € / authorization)**

Section 1 - 1 °: Request for modification / variation of a parallel import authorization
Application for modification of a parallel import authorization (with the exception of the modifications corresponding to Article 7 §2 and § 3): **€ 650.40 / authorization**

Parallel importation is based on European legislation (+ case law), but not on a specific regulation of medicines: except Article 28-30 of the EU Treaty on the 'free movement of goods'.

European Commission communication on parallel importation.

Useful links:

http://eur-lex.europa.eu/en/index.htm

http://curia.europa.eu/

Renewal:

In accordance with Article 9 of the Royal Decree of 3 July 1969 on the registration of medicinal products, the registration of a medicinal product was valid for 5 years and was renewable for a period of five years.

Any request for renewal of a national MA, granted either by the national procedure or by the MRP procedure, must be introduced **at least 9 months** before its expiry date The file should no longer include a periodic safety report, but should contain all the documents as described in Annex 3 of the "Best Practice Guide for Mutual Recognition and Decentralized Procedures"

Since 1 st January 2016 , the use of the electronic application form for the introduction of a renewal package of authorization on the market is required . This form is available at the following address: http://esubmission.ema.europa.eu/eaf/index.html.

The document for calculating the fee for a renewal can be consulted via the following link: https://www.fagg-afmps.be/sites/default/files/downloads/reg-EN-2016-01.pdf

EU pharmaceutical legislation - Hierarchy

Regulation – Binding to all Member States (MS), no national changes allowed (e.g. Paediatric Regulation)

Directive – Results binding but method up to MS, local interpretation (e.g. Clinical Trials Directive)

Guidelines – Interpretation of requirements, recommended but not binding (e.g. "Guideline on the readability of the labelling and package leaflet of medicinal products for human use")

Current Pharmaceutical Legislation

Directive 2001/83/EC - the core legislation governing the regulation of drugs in EU, provides the framework for regulation of medicines at national level

Regulation (EC) No 726/2004 – Sets out the centralised procedure

Legal basis for applications in the EU:

The following Articles of Directive 2001/83/EC gives the legal basis for various types of applications.

- Article 8(3) Full application i.e New Drug Application
- Generic, hybrid or similar biological applications - Article 10
  - Article 10a Well-established use application
  - Article 10b Fixed dose combination application
  - Article 10c Informed consent application

- Article 10(1) Generic application
- Article 10(3) Hybrid application
- Article 10(4) Similar biological application

Article 8(3) - Full application:

For full applications according to Article 8(3) of Directive 2001/83/EC, the results of pharmaceutical tests (physico-chemical, biological or microbiological), pre-clinical tests (pharmacological and toxicological), and clinical trials need to be submitted.

Article 10 - Generic, hybrid or similar biological applications:

Generic applications: Article 10(1)

According to Article 10(1) of Directive 2001/83/EC, the applicant is not required to provide the results of pre-clinical tests and clinical trials if he can demonstrate that the medicinal product is a generic medicinal product of a reference medicinal product which is or has been authorised under Article 6 of Directive 2001/83/EC for not less than 8 years in a Member State or in the Community.

A generic medicinal product is defined as a medicinal product that has:

- Same qualitative and quantitative composition in active substances as the reference product,
- Same pharmaceutical form as the reference medicinal product and
- Whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies.

It should be noted that the period of **8 years** from initial authorisation of the reference medicinal product, providing a period of so-called "**data exclusivity**", only applies to those reference medicinal products for which the initial application for authorisation was submitted through the centralised procedure after 20 November 2005.

Hybrid applications: Article 10(3)

Hybrid applications under Article 10(3) of Directive 2001/83/EC differ from generic applications in that the results of appropriate pre-clinical tests and clinical trials will be necessary in the following three circumstances:

- Where the strict definition of a 'generic medicinal product' is not met;
- Where the bioavailability studies cannot be used to demonstrate bioequivalence;
- Where there are changes in the active substance(s), therapeutic indications, strength, pharmaceutical form or route of administration of the generic product compared to the reference medicinal product.

These applications will thus rely in part on the results of pre-clinical tests and clinical trials for a reference product and in part on new data.

Similar biological application: Article 10(4)

In Article 10(4) of Directive 2001/83/EC it is stated that where a biological medicinal product which is similar to a reference biological product, does not meet the conditions in the definition

of generic medicinal products, owing to, in particular, differences relating to raw materials or differences in manufacturing processes of the similar biological medicinal product and the reference biological medicinal product, the results of appropriate pre-clinical tests or clinical trials relating to these conditions must be provided.

Well-established use application: Article 10a

According to Article 10a of Directive 2001/83/EC, it is possible to replace results of preclinical and clinical trials by detailed references to published scientific literature (information available in the public domain) if it can be demonstrated that the active substances of a medicinal product havebeen in well-established medicinal use within the Community for at least 10 years, with recognised efficacy and an acceptable level of safety.

Applicants should submit Modules 1, 2 and 3. For Modules 4 and 5, a detailed scientific bibliography shall address all required pre-clinical and clinical characteristics, and should be summarised in Module 2.

It should be noted that, if well-known substances are used for entirely new therapeutic indications, it is not possible to solely refer to a well-established use and additional data on the new therapeutic indication together with appropriate pre-clinical and human safety data should be provided. In such case, Article 8(3) of Directive 2001/83/EC should be used as legal basis.

Fixed combination application- Article 10b

According to Article 10b of Directive 2001/83/EC, in the case of medicinal products containing active substances used in the composition of authorised medicinal products but not hitherto used in combination for therapeutic purposes, the results of new pre-clinical tests or new clinical trials relating to that combination shall be provided in accordance with Article 8(3)(i) of the same Directive, but it shall not be necessary to provide scientific references relating to each individual active substance.

The combination of active substances within a single pharmaceutical form of administration according to this provision is a so-called 'fixed combination'.

Applications for fixed combination medicinal products can be accepted and validated under Article 10b on condition that the individual substances have been authorised as a medicinal product in the EEA via a Community or national procedure.

A full dossier, comprising all the information of modules 1 to 5, has to be provided in relation to the fixed combination. Any absence of specific fixed combination data should be duly justified in the Non-clinical and/or clinical Overviews.

Informed consent application- Article 10c

According to Article 10c of Directive 2001/83/EC, following the granting of a marketing authorisation, the authorisation holder may allow use to be made of the pharmaceutical, non-clinical and clinical documentation contained in the dossier of the medicinal product for the purpose of examining subsequent applications relating to other medicinal products possessing

the same qualitative and quantitative composition in terms of active substances and the same pharmaceutical form.

It is a prerequisite for the use of Article 10c as legal basis that consent has been obtained from the marketing authorisation holder of the reference product for all three modules containing the pharmaceutical, pre-clinical and clinical data (modules 3, 4 and 5), and the applicant of the informed consent application should have permanently access to this documentation or should be in possession of the information.

For such informed consent applications, only a complete module 1 should be submitted, including the Application Form with relevant Annexes (e.g. copy of correspondence with the European Commission for multiple applications, if applicable, and the letter of consent from the MAH of the authorised medicinal product allowing access to modules 2, 3, 4, 5 of the initial dossier and any subsequent documentation submitted)

If the dossier of the authorised medicinal product includes an ASMF, a new letter of access should be included in module 1 of the informed consent application.

Data exclusivity, market protection and paediatric rewards

Data exclusivity: 08 Yrs

Period of time during which a Company cannot cross-refer to the data in support of another marketing authorisation, i.e.: generics, hybrids, biosimilars cannot be validated by the Agency

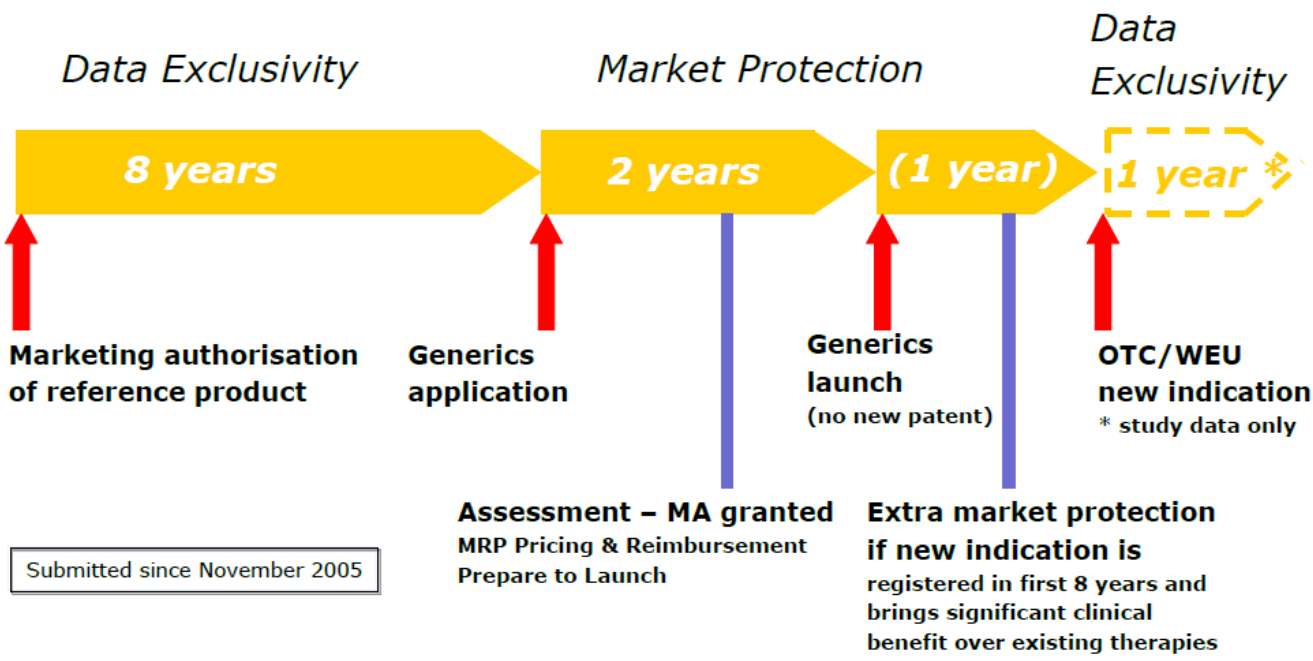
Market protection: 02 Yrs

Period of time during which a generic, hybrid or biosimilar cannot be placed on the market, even if the medicinal product has already received a marketing authorisation.

+1 year market protection for a new therapeutic indication which brings significant benefit in comparison with existing therapies (Art. 14(11) Reg. (EC) No 726/2004) - *For initial MAA and authorisation of new indication within 8 years*

+ 1 year data exclusivity for a new therapeutic indication for a well-established substance, provided that significant pre-clinical or clinical studies were carried out in relation to the new indication *(Art. 10(5) Dir. 2001/83/EC) (=+1 WEU)*

+1 year data exclusivity for a change in classification of a medicinal product on the basis of significant pre-clinical tests or clinical trials *(Art. 74(a) Dir. 2001/83/EC) (=+1 OTC switch)*



Orphan Drugs: 10 Yrs Market Exclusivity

Orphan designation criteria

- Rarity of condition (< 5 in 10,000) or insufficient return on investment
- Seriousness of condition (Life threatening/chronically debilitating)
- Existence of satisfactory methods

Paediatric Exclusivity: **Six-month extension** to the product's SPC (Supplementary protection certificate)

Paediatric orphan Drugs: **12 Yrs Market Exclusivity**.

Paediatric Use Marketing Authorization (PUMA):

For products developed exclusively for use in the paediatric population

8 Yrs - Data Exclusivity and

10 Yrs - Marketing Exclusivity

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.

For the national procedure, in the absence of opposition within 10 working days of receipt of a validated notification, the change may be applied. For the mutual recognition procedure, the approval period is set by the reference Member State (RMS).

The following national administrative variations are treated as variations of type IA (Article 34 §1 of the Royal Decree of 14.12.2006): a modification of the marketing authorization holder, a modification of the linguistic role and a modification of the wholesale distributor.

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

For the national procedure, in the absence of opposition within 30 days of receipt of a validated notification, the change may be applied. For the mutual recognition procedure, the approval period is set by the reference Member State.

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

For the national procedure, a period of 60 days is provided for the examination of these applications. It can be extended to 90 days for changes regarding the change or addition of therapeutic indications. These deadlines may also be extended by 30 days if the Commission for Medicinal Products for Human Use (CMH) deems it necessary.

For the mutual recognition procedure, the approval period is set by the reference Member State.

National Modifications Type II of Module 3: Clarification of the evaluation strategy

Type II changes involving revision of sections 4.6, 5.3 and 6.6 of the SPC: Guidance (23/12/2011)

Clinical variations of type II in the national procedure "Out of scope comments" -v.2.2 (10/05/2012)

Readability User Testing

Since May 26, 2006, applications for a MA for medicinal products for human use must include the evidence and the result of the consultation of groups of patients with regard to the readability of the package leaflet (Article 6 (1d), fourth paragraph of the Law on medication). This consultation of patient groups can take place in any Member State and therefore also in any language. The report on the results of this consultation must be in one of the three national languages or in English.

For MA applications and MAs introduced or granted before 26 May 2006, the Royal Decree of 14 December 2006 (part 1 - part 2) provides for a transitional period of 5 years to comply with these provisions.

To help MAHs comply with these legal requirements, the FAMHP has drafted a Q & A document .

Extension of market Authorizations:

Certain changes to a marketing authorization, however, have to be considered to fundamentally alter the terms of this authorization and therefore cannot be granted following a variation procedure. These changes are to be submitted as 'Extensions of marketing authorizations.
Three main categories of 'changes requiring an extension of marketing authorization:

- Changes to the active substance;
- Changes to the strength, pharmaceutical form and route of administration;
- Other changes specific to veterinary medicinal products to be administered to food-producing animals or change or addition of target species.

Detailed guidelines on variations/Extensions (European Medicines Agency post-authorisation procedural advice for users of the centralised procedure) can be identified @ http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500003981.pdf

Sunset Clause:

The so-called "sunset clause" is a provision leading to the cessation of the validity of the marketing authorization if:

- The medicinal product is not placed on the market within three years of the authorization being granted or,
- Where a medicinal product previously placed on the market is no longer actually present on the market for three consecutive years.

The European Commission may grant exemptions on public health grounds and in exceptional circumstances if duly justified.

Fees payable to the EMA for Marketing Authorizations through CP

Fee type	Human medicines	Veterinary medicines
Marketing-authorization application (single strength, one pharmaceutical form, one presentation) For New drug Application	From €286,900	From €143,700
For Similar Biological Application (Article. 10(4) Application)	From €185 500	Full fee – Immunologicals- 71 400
For Generic/Hybrid/Informed Consent Applications: (Article 10(1), Article 10(3) and Article 10c Applications)	From €111 400	
Extension of marketing authorization(level I)	€86,100	€35,900
Type-II variation (major variation)	€86,100	€43,000
Renewal of a marketing authorisation, For each strength associated with a pharmaceutical form	€14 200	€7 200
Inspection Fee	€21 600	€21 600

Scientific advice	From €43,000 to €86,100	From €14,200 to 43,000
Annual fee (level I)	€102,900	€34,400
(Level III)- For of generic, hybrid or informed consent medicinal product (Articles 10(1), 10(3)	€25 600	€8 500
Establishment of MRLs	-	€71,400

Full details on all fees and fee reductions are available in: Explanatory note on general fees payable to the EMA as of 1 April 2018.

Fees payable to the AFMPS

The remuneration to be paid upon submission of your application is shown in the table of fees and legally fixed by Article 28 and Annex VII, Title 1 st , Chapter 1 st , Section 1 st of the law of 11 March 2018 on the financing of the Federal Agency for Medicines and Health Products. Always include in your file the completed ad-hoc form , indicating the remuneration paid.

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Details of importing country embassy in India: https://india.diplomatie.belgium.be/en/embassy-new-delhi

Contact details of Indian Embassy abroad: https://www.indianembassybrussels.gov.in/

List of Local Pharma Associations:

- The Belgian Pharmaceutical Industry Association (AGIM-AVGI) https://pharma.be/nl/