Pharmaceuticals Export Promotion Council of India

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

REGULATORY & MARKET PROFILE OF FRANCE

DEMOGRAPHY

SL. No	Parameter	Description
1	Region	Europe
2	Country	France
3	Capital	Paris
4	Population	67,106,151 (July 2017 est.)
5	Population growth rate (%)	0.39% (2017 est.)
6	GDP (purchasing power parity)	$ 2.836 Trillion (2017 est.)
7	GDP - real growth rate (%)	1.9% (2017 est.)
8	GDP - per capita (PPP)	$ 43,600 (2017 est.)
9	Epidemiology	Cancer, Cardiovascular diseases, Neurological disorders, Diabetes, urogenital, Blood and Endocrine diseases and Chronic Respiratory diseases
10	Population below poverty line	14.2%(As per 2015, No update)
11	Age structure (%)	0-14 years: 18.53%
		15-24 years: 11.79%
		25-54 years: 37.8%
		55-65 years : 12.42%
		65 & above: 19.48%
Source: CIA World Fact Book updated to july 2017		

MARKET REPORT

Introduction

Recent Government measures seem to encourage research oriented companies of the country and try to reintroduce the spirit of competitiveness which was almost lost during the recent times. Government is accelerating the process of granting market authorisation of innovative medicine as well as market access.

Market has touched $ 41.0 billion in 2017 and is forecasted to grow to $ 44.3 billion with 8% growth.

Latest Updates

- In July 2018, Prime Minister Edouard Philippe announced measures to improve the attractiveness of France for the health industries, guaranteeing them a minimum growth in drug spending over three years and simplified administrative procedures to launch new products or conduct clinical trials.
- In addition, the Temporary Use Authorization (ATU) mechanism, allowing patients to access particularly innovative medicines before price negotiations are finalized, will also be used for extensions of therapeutic indications of the same treatment, an adaptation which became evident in view of the progress of immunotherapies.
- A focus on access to health data and the strengthening of big data capacity as well increased funds to health innovative projects through public and private funding of around EUR2bn managed by Bpifrance, is expected.
- Also in July, the government established a new Senate task force to investigate and address the increasingly concerning issue of medicine shortages

Strengths:

- One of the largest Pharma markets.
- A country with high percapita medicine spending and also high Prescription issuance by percapita.
- Transparent regulatory environment, based on EU directives.

Weaknesses

- Market growth in France has come under pressure due to government cost-control measures, including in terms of drug pricing and reimbursement.
- Low pharmaceutical prices have made France a popular source of parallel exports.
- Local research and development activity has been on the decline in recent years and many multinationals have closed their French research facilities in favour of lower-cost environments

Opportunities

- The government's pro-business agenda and lower corporation taxes to increase the market attractiveness to investors, including in the health sector.
- The government is poised to improve the pharmaceutical sector competitiveness as well as promoting innovation and clinical research.
- The potential for generic drug market growth in France is considerable, as the government expands cost containment and the number of patent expirations on blockbuster drugs increases.
- Reimbursement of certain OTC medications by insurance companies should provide stimulus for the growth of the OTC market.
- Ageing population stimulating demand for chronic treatments.

Market

Despite persistent cost-control measures targeting drug spending, France's pharmaceutical market growth rate is expected to accelerate during the next five to ten years, providing improved revenue-earning opportunities for Pharma companies. A large and ageing population, high per capita spending on medicines and continued efforts by the government to expand and improve access to healthcare will continue to secure France's position as one of the largest pharmaceutical markets worldwide.

The market is expected to grow from the present value of $ 41 billion with a cagr of 2.4% and reach a value of $ 46.25 billion by 2022.

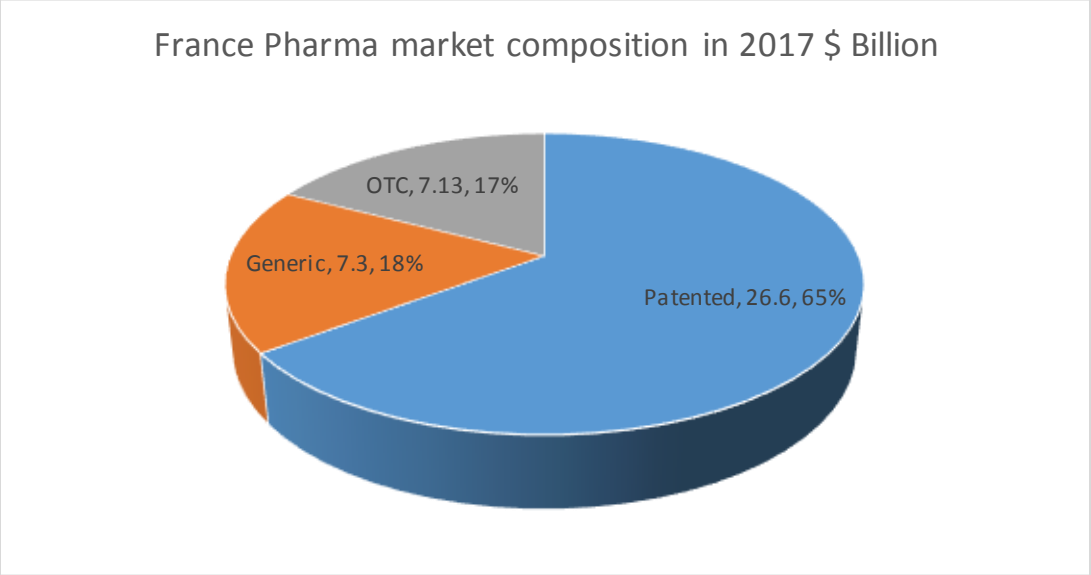
Cost-containment will remain high on the government's agenda and the pharmaceutical market will remain a target of cost containment, posing challenges to drug makers.

Although there are positive signs that the government will seek to strengthen the attractiveness of France for pharmaceutical firms and investors, the government's Loi de Financement de la Sécurité Sociale (LFSS - Social Security Finance Act) has consistently made the pharmaceutical industry a prime target for savings in its healthcare budget. According to the French Association of Pharmaceutical Companies (LEEM), of the EUR10bn (USD11.2bn) in cuts made by the government over a three-year period (the ONDAM three-year plan for 2015- 2017), EUR5bn (USD5.6bn) comes from pharmaceutical company contributions. Through this, they seek to highlight the extent of the contribution made by pharmaceutical companies to rebalancing the accounts of the National Goal of Health Insurance Spending (L'objectif national des dépenses d'assurance maladie - ONDAM). Macron has indicated that he will adhere to the previous government's ONDAM, which projects a slightly improved annual growth in healthcare spending of 2.3% in the period 2018-2022.

In fact the 2018 drug spending is expected to shoulder a burden of 25% of the savings expected by health insurance accounts. This might open some more opportunities for Generic producers though at reduced margins.

In recent years, savings from pharmaceutical spending were generated through price cuts, the increased use of generic medicines and biosimilars, discounts negotiated with drugmakers and changes to prescribing volumes. However, as of March 2016, according to the generic medicines association,

(GEMME), generic drugs penetration remains virtually stagnant in France, where less than a refundable medicine pack in three is a generic, against three in four in other European countries.



Generic Market

France's generic medicines market is expected to outpace the overall pharmaceutical market over the next five years, gaining share as a percentage of total drug sales. This is mainly explained by the patent cliff and the government's promotion of the use of generic medicines in place of more costly patented medicines.

Generic drug sales reached a value of USD7.30bn in 2017, and this is expected to increase to USD8.01bn in 2018. The 2017 generic drug market accounted for a still modest 17.8% of the total drug market by value. By 2022, sales are expected to reach USD8.86bn, observing a compound annual growth rate (CAGR) of 4.0%.

Patent expiration and the subsequent increase in the availability and consumption of low-value generic medicines in place of patented medicines are the important drivers of generic market. The growth rates are also due to the increased role of private finance in pharmaceutical purchasing, as well as the general promotion of the use of generic drugs, even though this appears to have been less than ideal.

As of March 2016, according to the generic medicines association, GEMME, generic drugs penetration remains virtually stagnant in France, where less than one in three refundable medicine packs is a generic, against three in four in other European countries. Following the announcement of price cuts for 2016, in June 2016 GEEM published an open letter to the Health Ministry stating that pricing pressure endangers the generic drug industry in France, which represents 15,000 employees. According to Erick Roche, President of GEMME, if the use of generic medicines in France reached a share equivalent to that found in other European countries, it would equal annually to USD1.6bn of additional savings for the health system.

Continuing to push for cost savings, as of January 2014, pharmacists in France were legally permitted to substitute a biosimilar in place of an originator biological medicine. This followed on from the signing of the 2014 Social Security Financing Law in December 2013, which allows for the automatic registration of a biosimilar on the biosimilar register as soon as its marketing authorisation has been granted by the French National Agency for Medicines and Health Products Safety (ANSM).

As in previous years, the health insurance spending targets and cost saving efforts for 2017 included encouraging the use of generics. In July 2017, the National Health Insurance Fund proposed good practices to reduce healthcare expenditure by EUR750mn, of which EUR150mn would be achieved through the adoption of generics or biosimilars.

In 2008, the senate approved an amendment to healthcare legislation that lowers the prices of generic medicines when they are found to be above the EU average. It was estimated that this would save health insurers approximately EUR130mn (USD163mn) a year.

Pharmaceutical Trade

Despite concerns over lagging competitiveness, France's positive pharmaceutical trade balance is expected to grow through the next five years. While rising domestic consumption will drive imports, an uptick in demand in the eurozone will support exports, as will the traditional positive effects on parallel exports driven by France's low prices.

In 2017 France’s exports are estimated to be $30.15 billion and is expected to go to $ 31.3 billion in 2018. Exports are expected to grow by 2.8% in the next five years.

Top export partners of France were Belgium, USA, Germany, Italy and Spain.

During 2017 Imports of France has touched $ 21.04 billion and is expected to go to $ 22.72 billion in 2018. Imports are likely to register a Cagr of 2.4% and touch $ 23.73 billion. Germany, The U.S. Switzerland, Belgium and The U.K. are the top importing partners.

Parallel trade has grown significantly in the EU over the past few years, with approximately 10% of medicine sales believed to occur through this practice

Risk/Reward Index

France’s multi-billion dollar drug market and large pensionable population results in the country scoring a high 80.9 out of 100 in BMI Innovative Pharmaceuticals Risk/Reward Index.

Epidemiology

Non communicable diseases or on the rise in the country akin to any other developed nation. Cancer is the most frequent cause of death in France (33.3% of total mortality), followed by cardiovascular diseases (32.5%), neurological disorders (8.4%), diabetes, urogenital, blood and endocrine diseases (6.2%), and chronic respiratory diseases (4.4%).

Indian company

In May 2007, Indian biotech firm Wockhardt acquired French pharmaceutical company Negma Laboratories for USD265mn. The deal made Wockhardt the largest Indian drugmaker operating in Europe. The region, with its appetite for low-cost generic products and high levels of health expenditure, is seen as a key target for Indian firms. Wockhardt has been expanding its presence in the continent gradually over the last few years, acquiring among others, UK-based CP Pharmaceuticals, Germany's Esparna and Ireland's Pinewood Laboratories.

Statistics

A) Exports

India's Pharmaceutical exports to FRANCE $ Million						
Category	**2015-16**	**2016-17**	**2017-18**	**GR%**	**contbn%**	**Contbn to Region**
BULK DRUGS AND DRUG INTERMEDIATES	70.31	56.55	57.53	1.73	22.88	6.38
DRUG FORMULATIONS AND BIOLOGICALS	147.36	134.39	175.44	30.54	69.77	10.86
AYUSH	1.75	2.72	3.75	37.65	1.49	16.77
Herbal Products	4.68	7.12	7.89	10.79	3.14	7.55
Surgicals	5.84	6.22	5.97	-4.04	2.37	5.74
Vaccines	1.83	1.86	0.86	-53.66	0.34	30.15
Total	231.76	208.87	251.44	20.38	100.00	9.14

B) Imports

Top Ten Importing Partners of France $ Million						
Rank	Country	2014	2015	2016	Gr%	Share%
1	Germany	3935.87	3508.86	3551.30	1.21	16.15
2	USA	4141.52	3924.99	3415.66	-12.98	15.53
3	Switzerland	1863.89	1822.92	2540.67	39.37	11.56
4	Ireland	2475.68	1871.81	1967.56	5.12	8.95
5	Belgium	4594.45	1716.47	1714.67	-0.10	7.80
6	Italy	1245.25	1134.14	1279.35	12.80	5.82
7	United Kingdom	1369.65	1031.10	1071.82	3.95	4.87
8	Spain	991.36	967.55	865.22	-10.58	3.94
9	Netherlands	833.78	699.67	806.83	15.32	3.67
10	Singapore	1108.20	986.42	790.82	-19.83	3.60
20	India	106.29	107.86	135.43	25.55	0.62
	World	27756.90	22120.51	21987.43	-0.60	100
Source: UN comtrade						

Regulatory Overview

The government's reform drive is increasingly concerned with modernising the health sector as well as transforming France into a highly attractive market for health industries and innovation.

Key legislation and regulatory authorities

Pharmaceutical products are supervised by several health agencies, the roles and responsibilities of which have been reorganised and harmonized in 2016, following the adoption of the Health Bill (Law No. 2016-41 of January 26 2016).

1. The National Agency for the Safety of Medicinal and Health Products (Agence Nationale de Sécurité du Médicament et des Produits de Santé, ANSM)'s main areas of responsibility include:

- Clinical trials.
- Marketing authorisations.
- Pharmaceutical establishment authorisations.
- Advertising.
- Pharmacovigilance. Import and export of healthcare products.

2. The National Authority for Health (Haute Autorité de santé, HAS) operates as a health technology assessment body. This key role in the regulation of the health system include:

- The scientific (medico economic) assessment of medicinal products, medical devices and procedures for price and reimbursement purposes.
- Drafting medico economic recommendations relating to healthcare strategies.
- Improving and supervising the quality of medical information to healthcare professionals and to the general public.

3. The Economic Committee for Health Products (Comité Économique des Produits de Santé, CEPS), in the Ministry of Health, is in charge of negotiating pricing agreements with pharmaceutical companies.

Regulatory Developments:

In July 2018, Prime Minister Edouard Philippe announced measures to improve the attractiveness of France for the health industries, guaranteeing them a minimum growth in drug spending over three years and simplified administrative procedures to launch new products or conduct clinical trials.

In addition, the Temporary Use Authorization (ATU) mechanism, allowing patients to access particularly innovative medicines before price negotiations are finalized, will also be used for extensions of therapeutic indications of the same treatment, an adaptation which became evident in view of the progress of immunotherapies.

In July 2017 Health Minister Agnès Buzyn stated that the third-party payer system will be updated and gradually generalized in order to prevent patients from having to pay consultation fees, deeming it a matter of equity and access to care since many French people reportedly give up seeking treatment because they do not want to advance money to a doctor.

REGISTRATION AND LICENSING REQUIREMENTS

➢	Regulatory Authority	:	**The National Agency for the Safety of Medicines and Health Products (ANSM)) / European Medicines Agency (EMA)**
➢	Website of regulatory Authority	:	https://www.ansm.sante.fr/ http://www.ema.europa.eu/
➢	Fees for Drug Registration	:	14,000 € 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
➢	Requirement of Local agent/ Subsidiary		Subsidiary is Required to operate locally

EMA Organization:

The European Medicines Agency (EMA) is a decentralised agency of the European Union (EU), located in London. 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.

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.

Once granted by the European Commission, the centralised marketing authorisation is valid in all EU Member States as well as in the EEA countries Iceland, Liechtenstein and Norway.

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.

National authorisation procedures

The majority of medicines available in the EU were authorised at national level, either because they were authorised before EMA's creation or they were not in the scope of the centralised procedure.

Each EU Member State has its own national authorisation procedures. Information about these can normally be found on the websites of the national competent authorities:

The list of Agencies responsible for regulation of medicines in Germany are:

Federal Institute for Drugs and Medical Devices	National Competent Authority for Human Drugs & Medical Device
Federal Office of Consumer Protection and Food Safety	Regulates Veterinary Medicines, Genetic Engineering, Foods, Fee, Consumer products, Pesticides I investigations.
Paul Ehrlich Institute	It promotes the quality, efficacy and safety of biomedical drugs through research and testing.

The National Agency for the Safety of Medicines and Health Products (ANSM)

About the ANSM:

The National Agency for the Safety of Medicines and Health Products (ANSM) was created by the law of 29 December 2011 on strengthening the safety of medicines and health products.

On 1 May 2012, ANSM replaced the French Agency for the Health Security of Medicines and Health Products (Afssaps), whose missions, rights and obligations it took over. It has been endowed with new responsibilities and missions, powers and strengthened means.

Activities:

- Authorizations for clinical trials (AEC) or substantial modifications (AMS)
- Regulates Pharmaceuticals, Biologicals, Herbals, Cosmetics, Homeopathic drugs, Blood related products,
- Regulated Narcotics & Psychotropic Substances
- Regulates Medical Devices
- Monitor (Vigilance activities)
- Control (laboratory control)
- Inspect on site
- Inform

Guidance document for Human Drug Authorization by ANSM can be identified at https://www.ansm.sante.fr/Activites/Autorisations-de-Mise-sur-le-Marche-AMM/Demande-initiale-d-AMM/(offset)/1

➢ The maximum period of examination of the application by the ANSM is 210 days from the submission of a complete application.

This period may be suspended in order to obtain the applicant for additional information, in this case, the instruction schedule reboots upon submission by the applicant for additional information. After evaluating the data folder of the Director General of ANSM can grant or refuse a marketing authorization.

Any submission to ANSM must include the following:

- Original submission cover letter (paper submission EN / IN);
- Two copies of the submission cover letter;
- Two copies of the Application Form;
- In case of electronic submission, the form to the structured electronic submission and validation report;
- A hard copy of the identification of the application form for the paper or electronic submission;
- Documents relating to the payment of taxes: receipt (s) and deposit slip receipts

- The complete file into a number of copies in accordance with the type of application and the chosen form for the submission

Electronic submission: CESP (Common European Submission Platform)

Electronic submission via CESP applies to initial MA applications as well as modification and renewal requests.

ECTD format

Mutual Recognition Procedures or Decentralized Procedure

- marketing authorization applications and modifications MA **from 1 st January 2018** : ANSM aligns the position of the EMA recommended the filing of eCTD electronic format

National Procedures

- Marketing authorization applications and modifications MA from **1 st January 2019:** ANSM recommends the filing of eCTD electronic format.
- Electronic format Nees is still accepted for all new applications for marketing authorization and marketing authorization changes **between the 1 st July 2018 and 31 December 2018**
- The abandonment of the paper format is recommended for all new MA applications and MA changes **as of 1 July 2018.**

Documents constituting an electronic submission to ANSM

1. CTD modules concerned on electronic media only
2. ANSM form for electronic submission
3. The original of the submission cover letter

A single letter per regulatory activity specifying:

- If there is an eCTD or an EU-NeeS;
- The sequence number if the deposit is in eCTD format;
- Confirmation that the bid is submitted in a single;
- Confirmation that the burning session was closed;
- Confirmation that the support has been scanned for viruses, negative before submission.

4. Two copies the accompanying letter of deposit.
5. For national procedure, an additional CD clearly separated and identified

   Applications must be accompanied by a proposal of appendices (I (SPC), II, IIIA (labeling) and IIIB (Note AMM / style sheet):
6. Documents relating to the payment of taxes
7. An identification of the application form
8. An electronic validation report
9. Two hard copies of the Application Form

Temporary Use Authorizations (ATU):

In France, the exceptional use of proprietary medicinal products not benefiting from a marketing authorization (MA) and not subject to a clinical trial is subject to the prior obtaining of a Temporary Authorization of 'Use (ATU).

Temporary Use Authorizations (ATU) are issued by the ANSM under the following conditions:

- The specialties are intended to treat, prevent or diagnose serious or rare diseases
- There is no appropriate treatment available on the market,
- Their effectiveness and safety of use are assumed in the state of scientific knowledge and the implementation of the treatment can not be postponed.

In practice, there are two types of temporary authorization of use: cohort ATUs and nominative ATUs.

Cohort ATU (ATUc)

- Concerns drugs whose effectiveness and safety of use are strongly presumed
- Is intended for a group or subgroup of patients treated and monitored according to criteria defined in a protocol for therapeutic use and collection of information (PUT).
- Is issued at the request of the holder of the exploitation rights, who has deposited or has committed to file a marketing authorization application within a fixed deadline.

Nominative ATU (ATUn)

- Addressed to a single patient named by name and unable to participate in biomedical research.
- Concerns drugs whose efficacy / safety ratio is presumed favorable for these patients in view of the available data.
- Is issued at the request and under the responsibility of the prescribing doctor if the drug is likely to be of benefit to this patient

Parallel distribution

The parallel distribution thus relates specialties:

- Benefiting from a Community marketing authorization valid in all Member States
- Whose qualitative and quantitative composition of active substance (s) and excipients, the pharmaceutical form and the therapeutic effects are therefore identical to those of the proprietary medicinal product marketed in France
- Which differ from one Member State to another only by:
  - ✓ The language version of the package leaflet and the labelling
  - ✓ The national specificities on the outer packaging (blue box or blue box) in addition to the information provided by the marketing authorization,
  - ✓ Where appropriate by the contents of the packaging actually marketed (presentation).

Controlling parallel distribution operations

The control of parallel distribution operations is the responsibility of the European Medicines Agency (EMA).

The parallel distributor has the obligation to:

- Report parallel distribution operations to the EMA.
- Notify the Agency and the marketing authorization holder of its intention to distribute in parallel in France a specialty benefiting from a Community MA. (application of the provisions of Article 76 (3) of the amended Directive 2001/83 / EC, as transposed to Article R. 5121-132-1 of the CSP)

Following this notification, the ANSM specifies in particular to the parallel distributor the specific national information that must be mentioned on the external packaging.

In addition, the operators involved in the pharmaceutical circuit followed by the distributed specialty must be authorized as a pharmaceutical establishment.

Parallel imports:

Parallel importation operations of pharmaceutical specialties result from the principle of free movement of goods between the States party to the Agreement on the European Economic Area.

Parallel Import Authorization:

Parallel import operations are subject to prior authorization, issued by the executive director of ANSM.

It can only be given when the quantitative and qualitative composition of active ingredients and excipients, the pharmaceutical form and the therapeutic effects of the imported specialty are identical to those of the specialty already authorized by the ANSM.

The excipients may nevertheless differ or be present in different quantities, provided that this has no therapeutic effect and does not pose a risk to public health.

In addition, the operators involved in the pharmaceutical circuit followed by the imported specialty must be authorized as a pharmaceutical establishment.

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

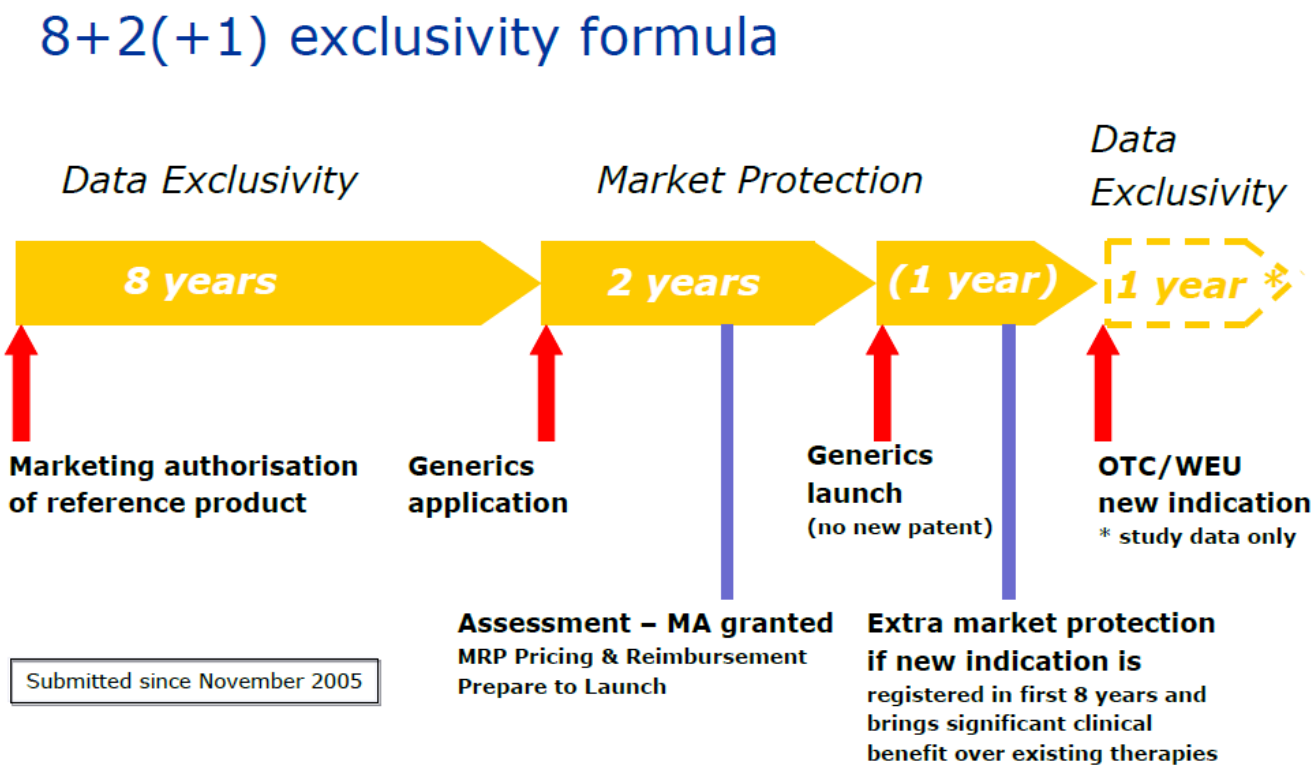
Market protection: 02 Yrs

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.

Type IB variations:

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

Examples of Type IB Variations

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

Type II variations:

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

Examples of Type II Variations

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

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 ANSM

ANSM fee for various kinds of applications can be identified at https://www.legifrance.gouv.fr/affichCodeArticle.do;jsessionid=39BB108786CFE5FCC30AB2B7B48E2727.tpdila10v_1?idArticle=LEGIARTI000030695761&cidTexte=LEGITEXT000006069574&categorieLien=id&dateTexte=20150701