ITALY
PHARMA MARKET
&
REGULATORY REPORT

Pharmaceuticals Export Promotion Council of India

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

CONTENTS

Demography

SL. No	Parameter	
1	Region	Southern Europe
2	Country	Italy
3	Capital	Rome
4	Population	62,402,659 (July 2020 est)
5	Population growth rate (%)	0.11%(2020 est)
6	GDP (purchasing power parity)	$ 2.317 trillion(2017 est.)
7	GDP - real growth rate (%)	1.5%(2017est)
8	GDP - per capita (PPP)	$38,200 (2017 est.)
9	Exchange rates	
10	Population below poverty line	29.9%(as per2102 data)
11	Age structure (%)	0-14 years: 13.45%
		15-24 years9.6%
		25-54years and over: 40.86%
		55-64 years 14%
		65 & above 22.08%
Source: CIA World Fact Book updated to july 2020(On 30th April 2020)		

MARKET REPORT

Introduction:

Italy's pharmaceutical market is likely to expand over the next five year period, driven by the rising demand for treatment by an ageing population as well as the introduction of new innovative therapies. Though this will translate into renewed commercial opportunities for Pharma companies, operating conditions will remain challenging due to cost-control measures targeting pharmaceutical and healthcare spending. In fact, despite the new government's populist leaning, fiscal loosening will not translate into a retrenchment from austerity measures aimed at controlling rising healthcare costs. Meanwhile, Italy's pharmaceutical production and exports will continue to observe robust growth over the coming years.

Pharmaceutical sales has registered a mark of $ 32.73 bn in 2019 with a negative growth of 3% and is forecasted to grow1.2 % in 2020 and reach $ 33.15 bn.

Updates

- In March 2020, Angelini Pharma experienced a sharp spike in sales of hand sanitiser due to the Covid-19 (coronavirus) outbreak. It was reported that stock that would usually sell out in two months had sold out in four days, driving the company to increase production to meet consumer demands as customers have requested stock directly from the manufacturing plant itself.
- In February 2020, the European Commission granted approval to Pfizer Italia for Vyndaqel (tafamidis) for the treatment (the first and only approved treatment in the EU) of acquired or hereditary transthyretin amyloidosis in adult patients with cardiomyopathy, a rare and life-threatening disease characterised by the accumulation of pathological deposits of cardiac amyloid and by restrictive cardiomyopathy and progressive heart failure.

- The Lombardy region in Italy, which went into lockdown in March 2020, has been searching for more medical personnel to assist with the Covid-19 (coronavirus) outbreak after around 10% of the already practising doctors and nurses have caught the coronavirus and hospitals are reportedly struggling to cope. So far, a few avenues pursued have been pulling doctors out of retirement and fast-tracking nursing students to assist.

- In March 2020, Angelini Pharma experienced a sharp spike in sales of hand sanitiser due to the coronavirus outbreak. It was reported that stock that would usually sell out in two months had sold out in four days, driving the company to a frenzy to increase production to meet consumer demands as customers have requested stock directly from the manufacturing plant itself.

Strengths:

- The Italian pharmaceuticals market is one of the top 10 largest markets in the world.
- Italy's regulatory environment, based on EU directives, is one of the most transparent in the world.
- Liberalization of OTC product sales since 2006.

Weaknesses:

- Government cost-cutting measures, including prescription drug price cuts and reimbursement delisting, restrict market growth.
- Wide regional variations in reimbursement and co-payment policies.

Opportunities

- The potential for generics market growth is immense, especially as the government's cost-containment policy will continue to push for the generics market expansion. However, Italy is a strong generic producer.
- An ageing population will continue to boost the demand for high-value medicines even among generics.

Market Overview

Italy is one of the major pharmaceutical markets in Europe. The pharmaceutical industry is Italy's most competitive manufacturing sector, above the beverage, chemical and machinery industries. It is also the most productive industrial sector in Italy. The Lombardy region ranks first for the number of people employed in the pharmaceutical industry (28,000 people).

77.5% of Pharma spending of the country is incurred by National health Services (SSN). Most of the growth in Pharma spending is due to Hospital Drug expenditure on Class 'A' drug including Essential drugs and drugs for chronic conditions. CVS drugs account as an entity as the largest group among hospital drug expenditure.

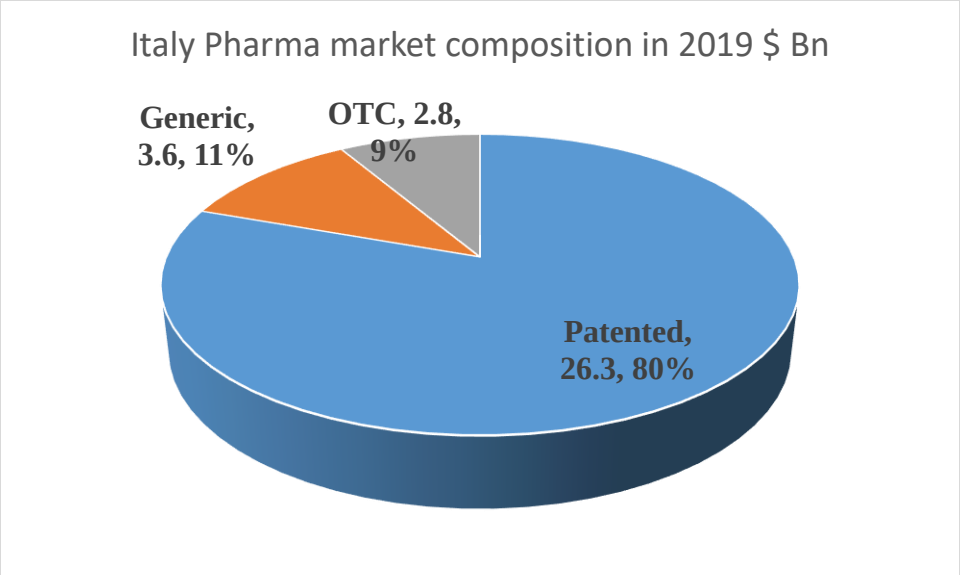
Despite the relatively rapid uptake of innovative pharmaceuticals, like many other developed states, Italy is introducing cost-containment measures that will restrict the commercial opportunities presented to drugmakers.

Market is expected to touch $ 36.3 Bn by 2024 with growth of Cagr of 2.1%.

Prescription drug spending accounted for 90.8% of total drug spending in 2017, valued at USD30.43bn. Patented drug spending reached USD27.03bn and generic drug spending was valued at USD3.39bn.

Non-communicable diseases - such as diabetes, cancer, asthma and cardiovascular conditions - account for the majority of the of the total disease burden.

Italy's pharmaceuticals market is fragmented, with most major multinationals having manufacturing facilities in the country. The five leading multinationals globally - GlaxoSmithKline, Merck, Novartis, Pfizer and Sanofi are all present on the Italian market with local production facilities. In terms of domestic companies, Recordati is one of the leaders. Two of the above multinationals(Pfizer & Sanofi) are having Generic subsidiaries which world leaders.



Generic Market

The implementation of measures to contain public expenditure on medicines, such as tough drug approvals criteria and drug expenditure ceilings, will challenge innovative drug companies selling products in Italy. Additionally, while the government is gearing policies towards increasing the use of lower-value generic medicines, the sector will experience sluggish growth as a result of price pressures on off-patented medicines.

In 2019, generic drug sales reached a value of USD3.6bn, representing just 11% of the overall market by value and has negatively grown by 0.19%. By 2024, it is expected that the generic drug market will be worth USD4.6bn and would constitute over 5.5%. This forecast takes into account Government's increased focus on cost containment in the healthcare sector and the direct role it aims to play in controlling expenditure on medicines and increasing the usage of generic medicines.

A report on Italian generic medicines states that Italy is among the European countries with the lowest uptake of generic medicines. Fast market entrance of generic medicines in Italy is hindered by several factors: the existence of Complementary Protection Certificates in the past. The report also stated that prices of generic medicines in Italy are low compared to other European countries. To contain pharmaceutical expenditure, pharmaceutical companies are currently forced to pay back in case of overspending, which disproportionally penalises small and fast growing companies, to which most generic companies belong to. Current demand-side policies do not successfully stimulate the use of generic medicines. The current market environment surrounding the Italian generic medicines retail market (ie, low prices, low volumes) threatens its long-term sustainability.

A recent report also states that perceptions of patients and professionals remain the major obstacles to increasing the use of generic medicines in Italy.

Pharmaceutical Trade

Italy is one among the few nations with positive trade balance in Pharma.

As per BMI, Italy's pharmaceutical exports reached a value of USD26.2bn in 2019. Pharmaceutical imports were valued at USD25.7bn in the same year. Due to domestic price controls, increasing numbers of Italian drug manufacturers are seeking to maximize their revenues on international markets. Recordati has expanded in Turkey and the Commonwealth of Independent States, as a result of difficult operating conditions on the home market. A number of multinationals have production plants in Italy and export drugs to other European countries.

Import volumes are likely to rise steadily as the market remains reliant on foreign drugs to meet certain epidemiological needs. The leading sources for pharmaceutical imports to Italy include Switzerland, Germany, France the UK and the US, although India and China to expected to play a greater role in future as their domestic industries grow and as more multinationals outsource production to Asia.

Statistics:

India's Exports

India Pharma exports to ITALY by Category $ Million					
Category	2015-16	2016-17	2017-18	2018-19	Change%
Bulk Drugs & Drug Intermediates	88.00	81.42	93.32	98.16	5.19
Drug Formulations & Biologicals	15.94	20.34	31.70	40.53	27.86
Ayush	1.07	1.62	1.27	1.95	52.81
Herbal Products	13.18	14.49	18.62	16.66	-10.56
surgicals	4.81	5.80	8.72	9.38	7.63
Vaccines	0.00	0.01	0.01	0.01	70.49
Total	122.99	123.67	153.64	166.70	8.50

India's Pharma exports to Italy $ Million			
Category	Fy-19	Fy-20	Change%
Bulk Drugs & Drug Intermediates	98.16	81.52	-16.96
Drug formulations & Biologicals	40.51	37.38	-7.73
Ayush	1.95	1.32	-32.04
Herbal Products	16.66	16.94	1.70
surgicals	9.40	8.92	-5.09
Vaccines	0.03	0.05	73.87
Total	166.70	146.13	-12.34

Italy Generic market negatively Grew in 2019 due to price controls, which is one of the reasons for India's generic exports negatively growing, besides the uncertainties of changes in EU.

Imports of Italy

Italy's top Ten formulations importing partners $ mn						
Rank	**Country**	**2016**	**2017**	**2018**	**Gr%**	**Contbn%**
1	Germany	2513.67	3578.32	5280.20	47.56	19.68
2	Belgium	3469.94	3373.29	4073.41	20.75	15.18
3	USA	3973.23	3705.36	3541.04	-4.43	13.20
4	France	2285.07	2476.00	3030.58	22.40	11.29
5	Switzerland	2482.15	2652.84	2497.91	-5.84	9.31
6	Netherlands	1431.61	1688.61	2161.92	28.03	8.06
7	Ireland	1435.37	1878.64	2110.13	12.32	7.86
8	United Kingdom	1159.05	1285.94	1179.49	-8.28	4.40
9	Spain	663.34	583.16	547.27	-6.15	2.04
10	Denmark	340.19	431.18	430.81	-0.09	1.61
25	India	23.47	35.18	42.57	21.02	0.16
	World	21311.86	23476.17	26835.06	14.31	100.00
Source: Uncomtrade						

REGISTRATION AND REGULATORY REQUIREMENTS

➢	Regulatory Authority	**:**	**AIFA** **Agenzia Italiana del Farmaco (Italian Medicines Agency) /** **European Medicines Agency (EMA)**
➢	Website of regulatory Authority	:	https://www.aifa.gov.it/ http://www.agenziafarmaco.gov.it/en http://www.ema.europa.eu/
➢	Fees for Drug Registration	:	26, 446 € 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

Regulatory Review

The main regulatory authority in Italy is the Ministry of Health. All products must be registered with the Ministry of Health's pharmaceuticals committee, the Commissione Unica sur Farmaco (CUF). In market regulation, the key agency is the non-independent AIFA. Market regulation is based on EU Directives 65/65/EEC, 75/318/EEC and 75/319/EEC, and as such, the operating environment should be considered fair and transparent. However, understaffing is causing delays to the processing of drug authorization applications - for which the maximum period is legally defined at 210 days.

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.

The Italian Medicines Agency (AIFA)

The Italian Medicines Agency (AIFA) is the national authority responsible for drugs regulation in Italy.
It is a public body operating autonomously, transparently and according to cost-effectiveness criteria, under the direction of the Ministry of Health and under the vigilance of the Ministry of Health and the Ministry of Economy.
It cooperates with the Regional Authorities, the National Institute of Health, Research Institutes, Patients' Associations, Health Professionals, Scientific Associations the Pharmaceutical Industry and the Distributors.

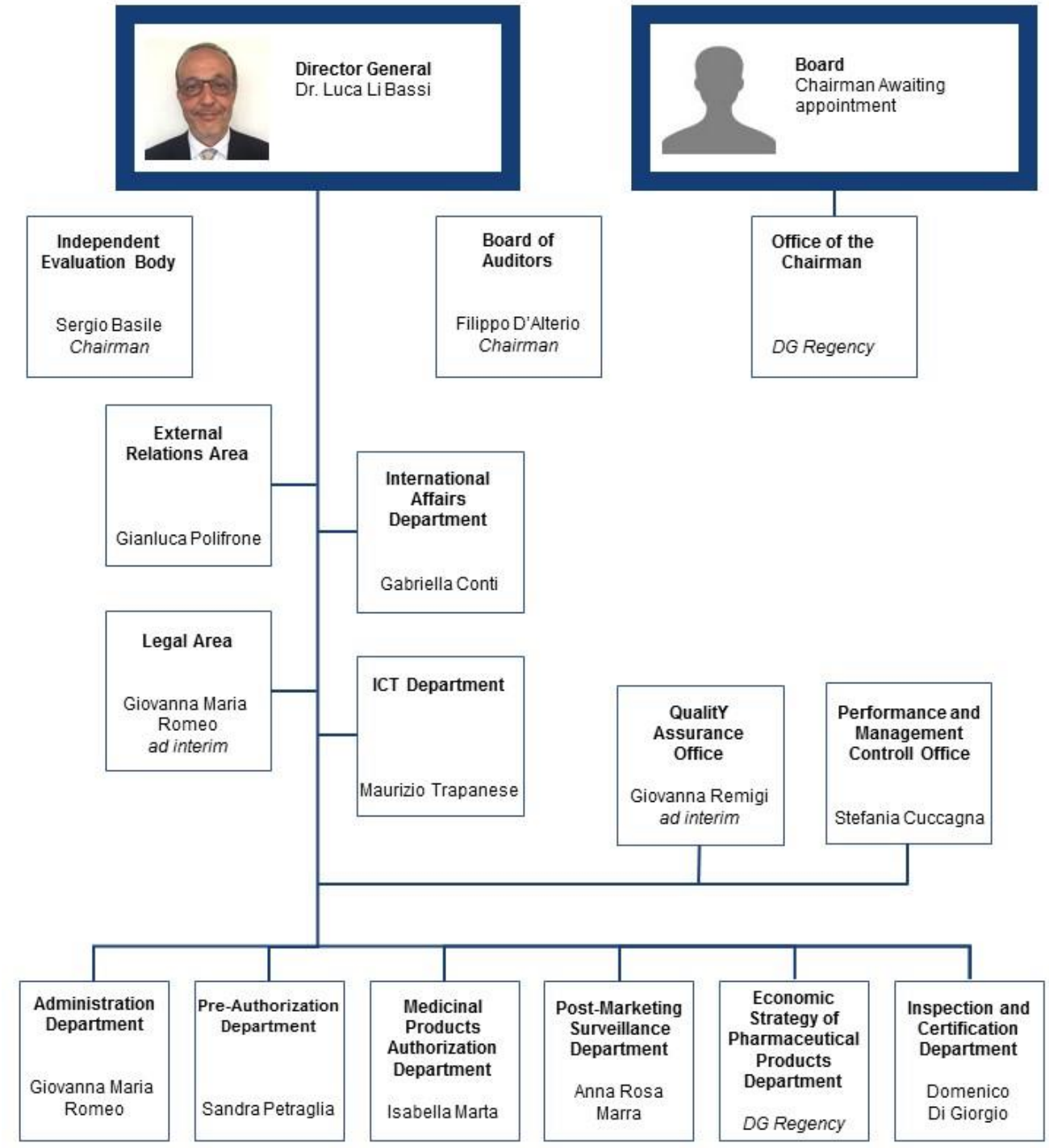
The mission:

- Promote good health through medicines
- Set fair pharmaceutical policies and assure their consistent application nationwide
- Manage the value and cost of medicines
- Promote pharmaceutical research and development
- Demonstrate independence and leadership both at home and internationally.

More specifically, the Agency:

- Guarantees access to medicines and their safe and appropriate use as means to protect public health.
- Ensures unity of the national pharmaceutical system in agreement with the regional authorities.
- Ensures innovation, efficiency and simplification of the marketing authorisation procedures, in order to grant rapid access to innovative drugs and to drugs used for rare diseases.
- Provides drug expenditure governance in the framework of economic and financial viability and competitiveness of the pharmaceutical industry.
- Encourages investments in research & development in Italy.
- Enforces the relationship with the Agencies of other member states, the European Medicines Agency (EMA) and other international bodies.
- Interacts with the community of patients' associations, the scientific medical world, pharmaceutical companies and distributors.
- Promotes pharmaceutical culture and knowledge.

Organization



Committees

The scientific authority and autonomy of the AIFA is supported by the activities of 4 Technical Scientific Committees consisting of experts of well-established experience.

Technical Scientific Committee*:* It assesses the national and European marketing authorisation applications, it delivers a consultative opinion on them and provides classification for reimbursement; the CTS takes over the tasks formerly attributed to the National Drug Evaluation Board (CUF, Commissione Unica del Farmaco) at the Ministry of Health.

Prices and Reimbursement Committee (CPR, Comitato Prezzi e Rimborso): It carries out the activity of negotiation with pharmaceutical companies for the setting of prices of medicinal products reimbursed by the National Health Service according to transparent methods, timelines and procedures established by the Interministerial Committee for Economic Planning (Comitato Interministeriale per la Programmazione Economia – CIPE) deliberation of 1st February 2001.

Observatories and databases

Observatories and databases are essential tools through which the Agency controls and analyses drug utilization at national, regional and local level, it monitors clinical trials approved by Local Ethics Committees and integrates the information obtained from the national pharmacovigilance network.

The Medicines Utilization Monitoring Centre (OsMED): It monitors drug prescriptions financed by the National Health Service and provides with monthly reports to the Regional Authorities according to pre-defined indicators on drug consumption and expenditure. It publishes the annual of the Drug Utilisation Monitoring Centrereport (in Italian).

The National Monitoring Centre for Clinical Trials (OsSC): Ensures the monitoring of all clinical trials conducted in Italy and approved by the Competent Authority and Local Ethics Committees. It manages the e-submission of CTAs and related substantial amendments for regulatory and ethics review, and the follow-up of administrative information (status/end of trial, summary of results); this observatory, is accessible to the Competent Authority, the Ethics Committees, the Regional Authorities and the Applicants. It publishes the annual report on clinical research in Italy, a brief summary of which is also available in English (Bulletin Clinical Trials of Drugs in Italy).

The National Monitoring Centre for Pharmacovigilance: It collects, through a national network, all the adverse drug reactions reports and supervises the risk-benefit profile of drugs; it is integrated with the European database EUDRAVigilance. It publishes an annual report on Pharmacovigilance in Italy.

REGISTRATION OF MEDICINES IN ITALY

In order to be marketed in Italy, a medicine must have been granted the Authorization for Trade Entry (AIC) by AIFA or the European Commission. The AIC is released following a scientific assessment of the quality, safety and efficacy requirements of the medicine.

In order to obtain the AIC, the applicant is obliged to submit an application consisting of a dossier containing information concerning chemical-pharmaceutical, preclinical and clinical aspects, structured in a standardized format (CTD - common technical document . The data and studies presented to support the AIC application must comply with guidelines and guidelines defined at European level.

The authorisation procedures provided by European law are:

- National procedure
- Mutual recognition procedure and decentralized procedure
- Centralized procedure
- Parallel import

Unless specifically appropriate, the AIC has a five-year renewable term for a further five years or indefinitely.

Through these procedures and supported by adequate software applications that ensure traceability, transparency and timeliness throughout the registration process, the Agency guarantees:

- Homogeneity of the pharmaceutical assistance over the national territory
- Access to innovative medicinal products and to drugs for rare diseases

The national procedure allows the marketing authorization of a medicinal product only in Italy, though assessment and registration process complies with the same criteria foreseen by the EU procedures, since the national legislation integrally implements the EU Directives.

The community procedures of marketing authorization of new medicinal products are divided into:

Mutual Recognition Procedure, allowing the extension of a marketing authorization granted by a Member State to one or more other Countries of the European Union.

Decentralized Procedure, allowing to obtain a single marketing authorization simultaneously valid in most countries of the European Union for a medicinal product which has been not yet authorized in Europe.

Activities

AIFA, through the **Assessment and Registration Unit**, is responsible for the activities related to administrative and technical-scientific assessment of documentation submitted for:

- ✓ New Marketing Authorization requests
- ✓ Variations to the terms of medicinal products already authorized.

In this context the Agency follows all the stages of the process, from the submission of the request to the final release of the marketing authorization (AIC), in accordance with the national procedures and with the Community ones in which Italy is the Reference or Concerned Member State (FORM_AIFA.RMS) - (Mod.309/2).

Such activities are performed for all categories of medicinal products for human use, included biologicals, human blood products, radiopharmaceuticals, medicinal gasses, herbals and homeopathic medicinal products.

Among the further activities related to national procedures, AIFA is competent for: Free Sale Certificates (Certificati di Libera Vendita - CLV or Certificati di Prodotto Farmaceutico - CPP), transfers of marketing authorization holder, depot and updating of DMF, import/export of plasma and human blood products, parallel imports of medicinal products, sale licenses, SIS code assignments.

Within the activities concerning the parallel import/export of medicinal products licensed according to the Mutual Recognition Procedure, AIFA provides the requesting Regulatory Authorities of the other Member States with information regarding some of the identification elements of the medicinal products authorized in Italy.

Aifa is also responsible for the application of the provisions related to the "sunset clause" for all medicinal products authorized in Italy.

Assessment

Within the assessment process, the Agency deals with the administrative and technical-scientific assessment of the dossier submitted for marketing authorization or variations to the terms of medicinal products for human use under national or Community procedure. The assessment aims at ensuring adequate standards of quality, safety and efficacy of all the medicinal products, through chemical, pharmaceutical, biological, pharma-toxicological and clinical assessments.

Such assessment is fulfilled with the assistance of the Technical Scientific Commission (CTS), with the co-operation of experts belonging to the National Institute of Health (ISS) and of other experts of well-known experience belonging to the Italian academic and health community. Moreover, the assessment activities are carried out in close collaboration with the other European countries involved in the assessment process and in accordance with the guidelines issued by the European Medicines Agency and the International Conference on Harmonisation - ICH, that in turns are periodically revised according to the latest ongoing updates in the scientific community. For this purpose AIFA is represented in all the relevant European seats.

Registration

The Agency takes care of finalizing the outcome of the positive assessment of medicinal products issuing the relative marketing authorization (AIC). Therefore, the UVA verifies the completeness and the propriety of the administrative dossier submitted for the requests and makes a linguistic review of the Summary of Product Characteristics, the patient information leaflet and the label of the medicinal products authorized under the Community procedure.

In order to ensure transparency in the authorization process a computerized system of transparency is available for the pharmaceutical companies, who can obtain online information about the progress of their requests of authorization and variations to the terms of authorization submitted to the AIFA, with regard to national, mutual recognition and decentralized procedures.

Medicinal Products Authorization Department
Head of office: **Isabella Marta**
E-mail: i.marta@aifa.gov.it

Centralised Authorisation Procedure/Community 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.

Please refer *Best Practice Guide for the Decentralised and Mutual Recognition Procedures (February 2020)*

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.

Submission of Applications where Italy acts as Reference Member State (RMS)

Any new request to AIFA to acts as RMS as well as any other application where Italy acts as RMS should be submitted according to the following procedure:

- For any marketing authorization application (including Line Extension and Repeat Use procedures) where Italy acts as RMS, please fill the forms **"FORM_AIFA.RMS"** and **"Mod.309/2"** and send them to the Head of the RMS&VAR Unit, Laura Braghiroli (l.braghiroli@aifa.gov.it). If the request is related to a biological product please send it in copy also to the Head of the MB Unit, Lorenzo Montrasio (l.Montrasio@aifa.gov.it).

- For variations, the Applicant is requested to inform the RMS in advance, by e-mail (at least 10 days before submission for type I and 20 days before submission for type II), sending the draft Application Form (AF) and the table of contents (ToC) and indicating the planned time for submission. All information should be sent to the contact point of the medicinal product, if already available, or otherwise to the Head of the IT-RMS and Variation Unit, Laura Braghiroli (l.braghiroli@aifa.gov.it) or, for biological product, to the Head of the MB Unit, Lorenzo Montrasio (l.Montrasio@aifa.gov.it).

Mandatory use of the CESP portal for the transmission of documentation regarding mutual recognition and decentralized procedures (27/06/2019)

National Authorization procedure

The AIC issued by national procedure is valid only in Italy. AIFA verifies the compliance of the documentation submitted by the company and verifies that the medicine is produced according to the standards of good manufacture, that its components (active ingredient and other constituents) are suitable and that the control methods used manufacturer are satisfactory.

With the support of the Scientific Technical Commission (CTS) and the Higher Institute of Health (ISS), AIFA evaluates the data presented by pharmaceutical companies on chemical-pharmaceutical, biological, biological, drug-toxicology and clinical on each drug intended to be placed on the Italian market, in order to ensure its safety and efficacy requirements.

These assessments, which begin at the first AIC, continue throughout the life cycle of the drug and for each subsequent modification of the authorisation (line extensions, extensions of therapeutic indications, etc.).

Public Reports of Evaluation of National AICs

For authorised medicines with a national procedure, AIFA makes Public Assessment Report (PAR) available on the data from pharmaceutical, preclinical and clinical trials contained in the documentation that the company presents AIC's application, subject to the deletion of all confidential business information.
The Public Assessment Reports, drawn up in the form prepared at European level, provide information on the medicine and its conditions of use. They reflect the scientific conclusions reached by AIFA in assessing the results of pharmaceutical, preclinical and clinical trials presented in the application documentation.
For equivalent medicines, the summary of the PARs of the reference medicine is also published, if the reference medicine has been authorised by national procedure. In other cases, the European Public Assessment Report (EPAR) published on the website of the European Medicines Agency (EMA) or the Agency acting as a reference member state (Reference Member State, RMS).
For approved medicines with a national procedure in the years prior to 2015, the Summary of Public Assessment Relations is published.

The Active Substance Master File (ASMF)

The applicant of the AIC, at the time of filing the application, is responsible for verifying that the manufacturer of the active ingredient has already filed ASMF with AIFA. The absence of ASMF means that the AIC application is not valid.
The owner of the ASMF must submit the following documents by postal service:

- Form of submission of the cover letter and administrative details (if the ASMF has previously been submitted to a competent authority, the owner of the ASMF is not required to resubmit it);
- The access letter, which should be identical except for the address of the relevant authority and include the commitment to inform the applicant and the EMA of any changes to the ASMF;

- ASMF (Participant Part, Restricted Party, General Quality Summaries and Expert Resume);
- General summary of separate or combined quality (QOS) for the applicant's parts and reserved parts;
- Copy of the expert's CV;
- A copy of the proposed ASMF holder's specification of the pharmaceutical substance (3.2.S.4.1);
- Proof of payment of fees.

The applicant's part, the restricted part of the ASMF and the general summary on the quality part must be presented in PDF format as individual files for the relevant sub-section of the CTD. All documents must be named according to the eCTD or NeeS conventions.

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.

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

Centralized Authorization Procedure :

The centralized procedure is coordinated by the EMA (European Medicines Agency), which works in network with the relevant authorities in each Member State. The authorization obtained in this way is valid in all EU countries and in the three states of the European Free Trade Association (EFTA) of the European Economic Area (EFTA): Iceland, Liechtenstein and Norway.

Through its Scientific Committee for Human Medicinal Products (CHMP), the EMA evaluates the documentation submitted by the pharmaceutical company, verifies the benefit-to-risk ratio based on the medicine's efficacy and safety data and expresses an opinion within a predefined time frame (maximum 210 days). The CHMP is made up of representatives from each Member State and experts selected on the basis of specific scientific expertise.

The evaluation process involves the active involvement of two Member States - (Co-)Rapporteur - which operate independently and a member state (peer reviewer) that verifies the quality of the assessments of the (Co)Rapporteur. The pharmaceutical company has the opportunity to respond to requests for clarification from the assessment and other Member States can comment.

The opinion expressed by the CHMP, by majority or unanimously, is sent to the European Commission, which issues a final decision on the AIC of the medicine with a binding character for all Member States.

Parallel Import and Deployment

Parallel imported medicines are drugs, registered and regularly on the market in a State of the European Union or the European Economic Area, for which AIFA, at the request of the importer, if there is a similar medicine on the market Italian, authorizes the import into our country.

The parallel import medicine has the same therapeutic effects and the same safety of use as the medicine authorized in Italy. The Summary of Product Features and the Parallel Import Medicine Illustration Sheet correspond to those of the medicine already authorized in Italy. Information about the owner and number of the AIC, the manufacturer, as well as, in some cases, the name and information on "How to store the medicine" and "Contents of the package and other information" may be different, including for the composition of the excipients. Parallel imported medicines have the instructions of the product and the importer on the outer packaging and in the Illustrative Sheet.

Parallel import of authorised drugs by national procedure, mutual recognition and decentralized Medicines of parallel import must have a valid AIC issued by the competent authority of the country of origin and be identical or similar to a product that has already received the AIC in Italy. The AIFA issues the Parallel Import Authorization (AIP), in a "simplified" procedure, by assigning a specific AIC code for the individual package to be imported, following the verification of the requirements of the legislation. To submit an AIP request, you must have a SIS code (identification code within the Healthcare Information System assigned by AIFA at the request of the company) and not be the AIC owner of the Italian reference product or company affiliated with it.

Parallel import applications (AIPs, changes to IPPs, renewals) are subject to a fee. Importers must also pay an annual right for each medicine with AIC in the process of being valid.

Parallel distribution of authorized drugs with centralized procedure

For authorized drugs with a centralized procedure, the evaluation of a parallel distribution application is conducted by the EMA. If successful, the EMA issues the importer with a Notice for Parallel Distribution indicating the country of origin and the country of origin (which can be more than one).

AIFA, at the request of the importer, verifies the EMA's authorization and assigns national identification data (description of the medicine to be imported, identification number, classification for reimbursement and supply).

Additional regulatory approvals

The Parallel Import Authorization is issued on the basis of the dossier submitted, except for the possession of additional regulatory authorizations:

- Authorization for the wholesale distribution of medicines issued by the autonomous regions and provinces, or by the relevant authorities identified by them;

- Authorizations issued by the relevant offices of the Ministry of Health, as in the case of drugs based on drugs or psychotropic substances.

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.

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 Pediatric 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

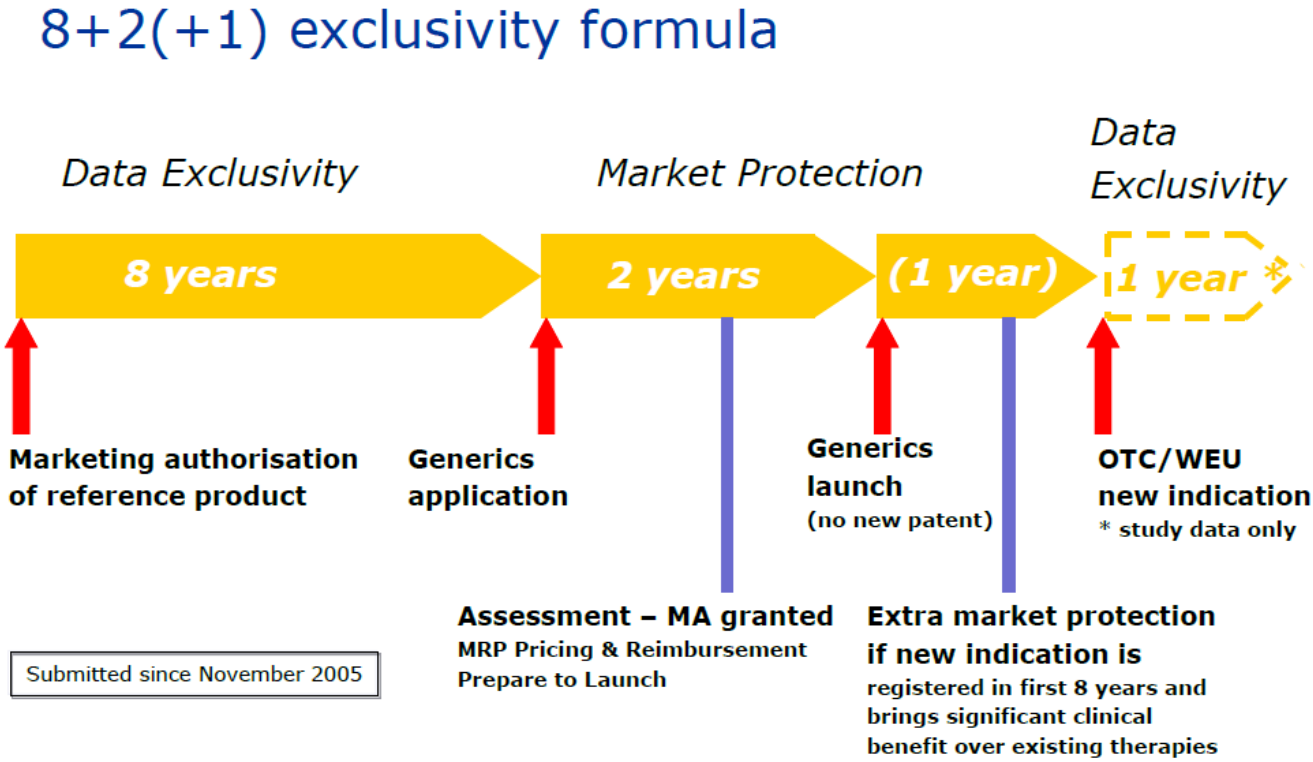
Market protection: 02 Yrs

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.

Fee Structure

Fees payable to the EMA for Marketing Authorizations through CP

Fee type	Human medicines	Veterinary medicines
Marketing-authorisation application (single strength, one pharmaceutical form, one presentation)	From €291,800	From €146,100
Extension of marketing authorisation (level I)	€87,600	€36,500
Type-II variation (major variation)	€87,600	€43,700
Scientific advice	From €43,700 to €87,600	From €14,400 to 43,700
Annual fee (level I)	€104,600	€35,000
Establishment of MRLs	-	€72,600

Full details on all fees and fee reductions are available in: Explanatory note on general fees payable to the EMA as of 1 April 2019.

Fees payable to the AIFA

Payment of annual fees and entitlements

From 1 April 2019, the rates contained in Annex 1 of D.M. 6 December 2016, concerning "Update existing tariffs and determine rates for unidated benefits", are automatically updated on the basis of the index ISTAT of the cost of living reported in December 2018, as required by art. 3, paragraph 1 of the same decree.

The updated rates apply to all applications or applications submitted as of April 1, 2019.

Rates paid prior to April 1, 2019 and relating to applications or applications submitted after that date, must be supplemented by matching the difference between what is paid and the new rate amount.

List of current tariffs in increments from January 2020 (Italian version) may be referred for fee structure by AIFA.

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- **Details of importing country Embassy in India**
  https://ambnewdelhi.esteri.it/ambasciata_newdelhi/en/

- **Contact details of Indian Embassy abroad**: http://www.indianembassyrome.gov.in/

List of Local Pharma Associations:

- Chemical Pharmaceutical Generic Association (CPA) http://www.cpa-italy.org/