Pharmaceuticals Export Promotion Council of India

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

REGULATORY & MARKET PROFILE OF GERMANY

DEMOGRAPHY

SL. No	Parameter	Description
1	Region	Europe
2	Country	Germany
3	Capital	Berlin
4	Population	80,594,017 (July 2017 est.)
5	Population growth rate (%)	-0.16% (2017 est.)
6	GDP (purchasing power parity)	$ 163.5 billion (2017 est.)
7	GDP - real growth rate (%)	5.1% (2017 est.)
8	GDP - per capita (PPP)	$ 3,500 (2017 est.)
9	Epidemiology	Cardiovascular Diseases, Cancer, Diabetes, Urogenital, Blood and Endocrine Diseases, Chronic Respiratory Diseases and Neurological Disorders.
10	Population below poverty line	36.1%(As per 2016, No update)
11	Age structure (%)	0-14 years: 12.82%
		15-24 years: 10.09%
		25-54 years: 40.45%
		55-65 years : 14.48%
		65 & above: 22.6%
Source: CIA World Fact Book updated to July 2017 on August 2018		

MARKET REPORT

Introduction

The German pharmaceutical market will continue to lead Western Europe in terms of commercial attractiveness. Substantial chronic disease burden, coupled with advanced healthcare infrastructure and easy access to services, will continue to support this potential. However, caution to be exercised as Government, like many others in Europe, are controlling costs through various measures. This has an impact on generics too.

Total Market was of the size $64.22 billion in 2017 having grown by 5%. It is forecasted to touch $ 69.42 billion by 2018 with a growth of 8%.

Latest in the industry

- Bayer is working with University of Texas, USA to help with their project of Novel targeted products for cancer therapy.
- Merck is working with SFJ Pharmaceuticals group of USA in developing abituzamab through innovative models for its use in colorectal cancer.
- In March 2018, the pharmacy association ABDA reported that an increasing number of patients are being prescribed marijuana, which was legalised in Germany in March 2017. According to the reports, health insurance agencies are also increasingly receiving applications for reimbursement of the costs associated with the use of medical marijuana, with 44,000 units of the plant already distributed to patients.

Strengths

- One of the key pharmaceutical markets in Western Europe.
- Germany's regulatory environment, based on EU directives, is one of the most transparent and fair in the world.
- High, long-term underlying demand for pharmaceuticals driven by the ageing population.
- One of highest rates of per capita spending on medicines in the world.
- Germany has a strong domestic pharmaceutical industry and several multinationals are also based in the country, with high rates of R&D in the sector

Weaknesses

- Market growth has been sluggish in recent years, largely due to increasingly harsh government cost-cutting measures, including de-reimbursement, a fixed-level drug price support scheme and reference pricing.

- Drug companies and health insurers must negotiate the prices of new drugs based on cost-effectiveness criteria, which discourages novel drug launches and thus disadvantages patients.
- German provinces have large autonomy regarding healthcare provision, requiring diverse access strategies

Opportunities

- The generic drug market is growing robustly, with the government's cost-containment policy and a significant number of patent expiries driving growth.
- Demographic and epidemiological profiles provide expansion opportunities for manufacturers of chronic treatments.
- Long-term economic rebalancing will translate into higher private consumption, posing upside risk to pharmaceuticals market growth.

Market

Despite cost containment measured adopted Germany is certainly a key market in the EU Region. Supportive epidemiological and demographic(more than 40% of the population would be requiring CNS drugs and over 50% would be requiring CVS drugs which are the prime generics) factors will continue to push up volume demand, with value growth.

Over the next five years ending 2022, the market is forecasted to grow at a cagr of 2.7% and reach $ 73.22 billion from $ 64.22 billion in 2017.

As is the case in most of Western Europe, an ageing German population is increasingly suffering from chronic conditions, which leads to higher demand for pharmaceuticals. This, in turn, places pressure on both public and private health funding regimes. As such, while volumes continue to grow, they are restrained by government cost-containment initiatives, including encouraging the consumption of lower-value generic drugs.

Generic Drug market

German generic drug sales will continue to benefit from cost-containment policies that have, as part of several objectives, encouraged their wider uptake in order to help control surging public healthcare costs.

Market in 2017 touched $ 12.20 billion and hold 19% share of the total market. It is expected to grow at a cagr of 3.5% and reach $ 14.54 billion by 2022 and attin a share of 19.4%.

Generic prescribing within the country's statutory health insurance system has significantly strengthened over the past three decades, currently accounting for an estimated 45-50% of all prescriptions. Indeed, various policy initiatives have overcome strong patient and prescriber bias towards branded medicines. Direct pressure on both groups for generic substitution comes from the pharmaceutical reimbursement system. For example, where a physician has prescribed a more

expensive branded drug, the pharmacist must inform the patient of the cheaper alternatives; the patient will have to pay the difference if he does not wish to take the generic.

Health insurance companies (Krankenkassen) award bulk tenders to drugmakers that charge the least for their products, resulting in a decline in the prices of off-patented medicines. As a result, Germany's generic drug market is gradually moving from a landscape dominated by a small number of high-value players(companies) to a commoditised market, made up of many players with lower value outputs. As commodity generics may be manufactured and marketed by numerous companies, buyers can obtain similar medicines from a number of approved sources. This necessarily forms an extremely price-competitive submarket within the already low-value generic medicines segment, however it si the health insurance payers who become the final deciding authority of purchase price from the companies.

Pharma Trade

Germany maintains a positive balance of trade, bolstered by strong exports of innovative pharmaceuticals. Despite the implementation of cost-containment measures affecting drug spending in Germany's major destination markets

Germany has exported $ 74.6 billion worth of Pharma in 2017 and is expected to post a cagr of 4.7% in the next five years ending 2022 and reach $ 93.75 billion.

Germany's leading export partners include Belgium, the US, Switzerland, France and the Netherlands.

Imports were put at $ 48.65 billion in 2017. This expected to increase at a cagr of 6% during the next five years and reach $ 64.96 billion.

The leading countries of origin for their imports include Switzerland, the UK, the US, France and Spain.

Risk/Reward Index

Germany's pharmaceutical market will remain a priority for innovative drugmakers. It remains ranked top in BMI's Western Europe region, which covers 15 markets. Its compound score is 82.5, thus falling significantly above the regional average which is 75.5. However, in addition to price freezes on medicines and mandatory discounts on drugs, Germany's health technology assessment and reimbursement decision-making bodies have taken an increasingly hard-line stance when determining whether a new drug provides added value to patients compared with existing therapies, via the Arzneimittelmarkt-Neuordnungsgesetz (AMNOG) legislation. This assessment will make actual newer introductions difficult to come by and ease the pressure a bit on existing products

Biotechnology Sector

The development of novel biotechnology, a key area of growth in Germany, has the potential to bring in substantial quantities of money both for the originating company and the countries that encourage

the research. Medical biotechnology industry clusters have developed organically in several regions of Germany. Federal and state initiatives are simultaneously promoting cooperation among players in various regions. The Munich Biotech Cluster, for example, has over 350 life science companies and was awarded a federal grant worth more than USD50mn to further support collaboration among companies, research institutes and other stakeholders. Cluster member MorphoSys AG recently signed an agreement with US-based ContraFect Corp to cooperate on the discovery and development of therapeutic antibodies for infectious diseases.

Around 150 companies are directly engaged in R&D of new drugs, either in preclinical or clinical area or as providers of technology platforms. Dr Norbert Gerbsch, deputy chief executive of the BPI, said: 'The new survey shows that the biotech industry is still in a strong position with its numerous pharmaceutical innovation powerhouses in Germany'.

Epidemiology

Non-communicable diseases are on the rise in Germany, while communicable diseases are expected to further increase through the next 15 years. Cardiovascular disease is the most frequent cause of death in Germany, followed by cancer, diabetes, urogenital, blood and endocrine diseases, chronic respiratory diseases and neurological disorders.

Pharma Industry

The German pharmaceutical industry is represented by four principal associations:

- The Association of Research-Based Pharmaceutical Manufacturers (VFA), which represents the interests of 44 global leaders in research-based pharmaceutical companies and more than 100 subsidiaries and affiliated companies in healthcare, research, and economic policy.
- The Association of the German Pharmaceutical Industry (BPI), which represents around 240 companies, including traditional pharmaceutical companies, pharmaceutical service providers, and companies in the fields of biotechnology, herbal medicine and homeopathy/anthroposophy.
- The Federal Trade Association of Pharmaceutical Manufacturers (BAH), which has more than 450 members who are primarily pharmaceutical producers, but also pharmacists, lawyers, publishers, agencies, as well as market and opinion research institutes in the healthcare field.
- Pro Generika, the association of companies that manufacture generic and biosimilar products, which has 16 member companies. Companies manufacturing generic and biosimilar products together cover over 75 percent of the medicinal drugs required by the statutory health insurance funds.

Statistics

Exports

India's Pharmaceutical exports to GERMANY $ Million						
Category	**2015-16**	**2016-17**	**2017-18**	**GR%**	**contbn %**	**Contbn to Region**
BULK DRUGS AND DRUG INTERMEDIATES	149.66	144.75	145.48	0.51	37.45	16.14
DRUG FORMULATIONS AND BIOLOGICALS	150.01	141.13	178.61	26.56	45.98	11.06
AYUSH	1.10	1.26	1.16	-7.82	0.30	5.20
Herbal Products	26.89	26.73	41.91	56.78	10.79	40.11
Surgicals	19.84	19.35	21.11	9.12	5.44	20.31
Vaccines	0.15	0.08	0.15	95.02	0.04	5.39
Total	347.65	333.30	388.43	16.54	100.00	14.12

Imports

Top Ten Importing Partners of Germany $ Million						
Rank	Country	2014	2015	2016	Gr%	Share%
1	Switzerland	8543.18	7190.48	8577.20	19.29	18.26
2	Netherlands	8607.39	8712.84	8274.23	-5.03	17.62
3	USA	7617.15	8657.46	7820.13	-9.67	16.65
4	Ireland	2394.37	2848.81	3364.33	18.10	7.16
5	Italy	2838.75	2046.37	2770.54	35.39	5.90
6	France	2948.78	2563.20	2506.24	-2.22	5.34
7	Belgium	3089.98	2108.65	2480.79	17.65	5.28
8	United Kingdom	2172.79	1963.79	2240.01	14.07	4.77
9	Austria	999.96	1138.21	1219.38	7.13	2.60
10	Spain	1322.34	1198.67	1087.86	-9.24	2.32
18	India	306.67	280.56	261.87	-6.66	0.56
	World	47490.67	44487.11	46962.38	5.56	100.00
Source: UN comtrade						

Regulatory Overview

The main regulatory authority in Germany is the Federal Institute for Drugs and Medical Devices (BfArM), and the Paul Ehrlich Institute (PEI). The PEI acts as the regulatory body for sera, vaccines, blood preparations, bone marrow preparations, tissue preparations, allergens, gene transfer medicinal products, somatic cell therapeutics, xenogenic cell therapeutics and genetically manufactured blood components. All pharmaceutical products available in the domestic market and those for export must receive authorisation from BfArM or PEI. The BfArM and PEI stipulate conditions on the basis of quality, safety and effectiveness.

The approvals system is fundamentally sound, especially compared to others globally. Given that Germany is part of the EU, products can be authorised through the National Procedure, the Centralised Procedure (CP), Decentralised Procedure (DCP) or Mutual Recognition Procedure (MRP). The number of products processed via the DCP has increased, whereas use of the MRP has tended to decline. The number of parallel imports has also decreased over the last few years.

The EU Directives 65/65/EEC, 75/318/EEC and 75/319/EEC form the basis for market regulation, with new EU regulation introduced in 2004. Directive 2011/62/EU, which amended directive 2001/83/EC, was due to have been implemented by all member states by January 2013. The new directive prevents falsified medicines from entering the supply chain, with measures that aim to increase safety measures across Europe including the following:

- Labels on the outer packaging of medicines to indicate authenticity;
- Strengthened requirements for the inspection of pharmaceutical manufacturers;
- Enforcing an obligation for manufacturers and distributors to report any suspicion of counterfeit medicines; and
- A logo appearing on the websites of online pharmacies with a link to official national registers.

All medicines are classed as either prescription or non-prescription on the basis of substance. Some herbal and OTC medicines can be sold outside pharmacies, with self-service also permitted. While prescription medicines cannot be advertised to the public, OTCs - including those that are reimbursed - may be advertised in all media. Advertising is regulated by the Medicine Advertising Act (HWG).

REGISTRATION AND LICENSING REQUIREMENTS

➢	Regulatory Authority	:	**The Federal Institute for Drugs and Medical Devices (BfArM) / European Medicines Agency (EMA)**
➢	Website of regulatory Authority	:	https://www.bfarm.de/ http://www.ema.europa.eu/
➢	Fees for Drug Registration	:	15,600 € 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 Federal Institute for Drugs and Medical Devices (BfArM)

About the BfArM:

The Federal Institute for Drugs and Medical Devices (BfArM) is an independent higher federal authority in the business area of the Federal Ministry of Health.

The BfArM has around 1,100 employees - including doctors, pharmacists, chemists, biologists, lawyers, engineers, technical assistants and administrative staff.

BfArM Tasks :

- Drug Approvals
- Pharmacovigilance
- Medical Devices
- Federal Opium Agency: Monitoring Narcotics & Commodity Traffic.
- Research

The legal basis of the authorization in Germany is Article 21 (1) of the **German Medicines Act (AMG)**, where the substantive requirements for the registration documents are laid down in Sections 22 to 24.

The components of the registration documents are analytical, pharmacological-toxicological and clinical tests as well as corresponding expert reports. In addition, the pharmaceutical company must provide its user and technical information, labelling texts and information on pack sizes. Last but not least, the exact description of the proposed pharmacovigilance or risk management system is part of the registration documents.

Instructions for submitting applications for authorization to the Federal Institute for Drugs and Medical Devices can be identified at https://www.bfarm.de/DE/Arzneimittel/Arzneimittelzulassung/Zulassungsverfahren/National/zul-einr-zul-antr_neu.html.

Renewals

Renewal of Marketing Authorizations and Registrations of Medicinal Products in Accordance with Sections 31, 39 of the German Medicines Act (Arzneimittelgesetz, AMG) and Art. 24 of Directive 2001/83/EC

Licenses and registrations are **valid for 5 years after granting**, unless an application for renewal is submitted at least 9 months prior to the expiry date.

Licenses and registrations that are renewed are not subject to a time limit, unless the competent superior federal authority orders a further renewal of 5 years in order to further guarantee the safe marketing of the medicinal product.

Parallel import of medicinal product

Pharmaceutical companies/manufacturers market many of their medicinal products in Germany as well as in other Member States of the European Union (EU) or the European Economic Area (EEA). For each of these products they hold a separate national marketing authorization in the respective Member State. A 'parallel imported medicinal product' is bought by a third company independent of the original marketing authorization holder (MAH) or manufacturer in another Member State of the EU or EEA and is imported into Germany to be marketed here in parallel to the product marketed by the original pharmaceutical company.

In economic terms, parallel import of pharmaceuticals is a consequence of the differing price levels for pharmaceuticals within the EU or EEA.

No parallel imported medicinal product may be imported or placed on the German market unless the company has received a corresponding license by the national competent authority for human medicinal products – i.e., either the BfArM (Federal Institute for Drugs and Medical Devices) or the PEI (Paul-Ehrlich-Institut). Parallel import is not possible if the medicinal product is authorized and marketed outside the EU or EEA.

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

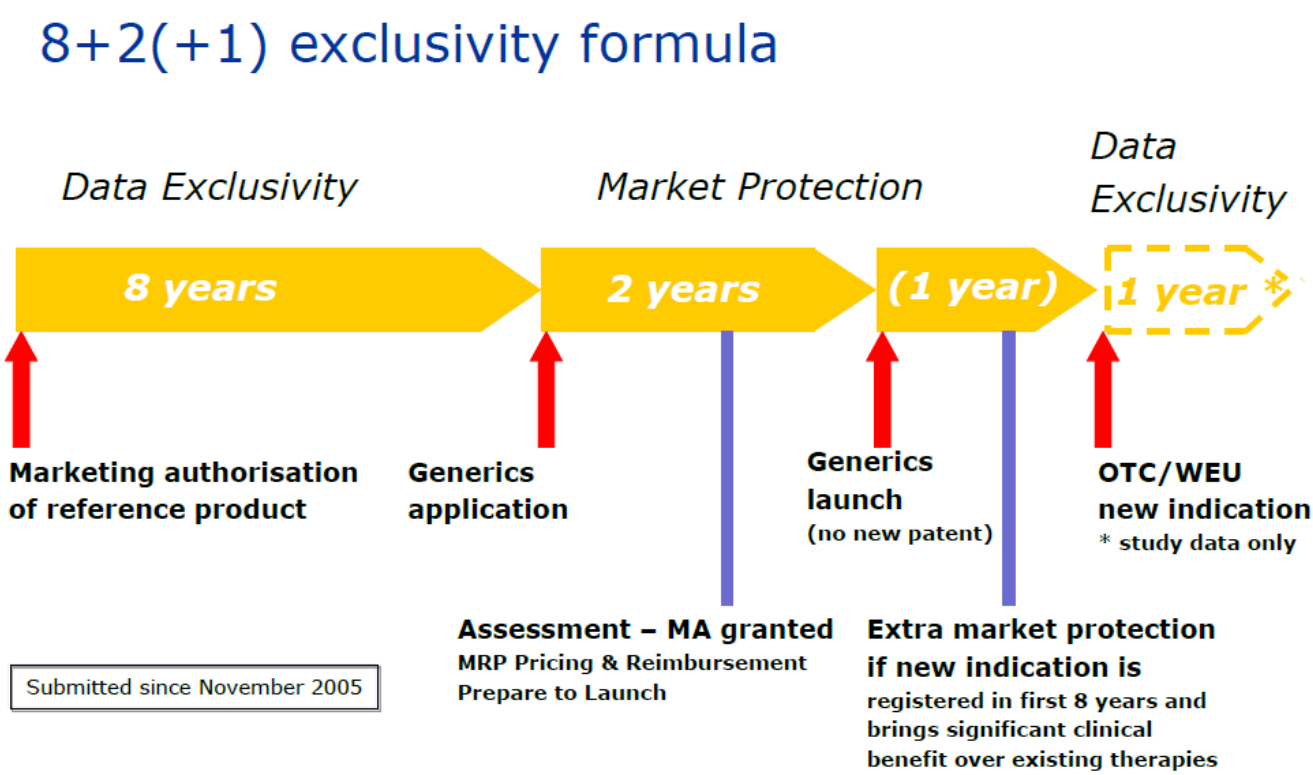
Market protection: 02 Yrs

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

Fees are adjusted every year for **inflation**. Fee **reductions and incentives** are available for micro, small and medium-sized enterprises (SMEs), designated orphan medicines, multiple applications on usage patent grounds and other classes of application. 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 BfArM

National Approval	
Authorization of medicinal products / new substance	From €51 100
Hybrid Applications	From €19 100
Generic Applications	From €15 600
Approval of a drug in the process of Mutual Recognition (MRP)	
With Germany as Reference Member State (RMS), in addition to the above fees	
Authorization of medicinal products / new substance	From €47 400
Hybrid Applications	From €22 500
Generic Applications	From €19 400
Approval of a drug from the Repeat Use Procedure (MRP another after an MRP after fees above for additional EU Member States)	
with new material	From €18 900
with a known substance	From €14 400
With Germany as the Member State concerned (CMS)	
Authorization of medicinal products / new substance	From €17 100
Hybrid Applications	From €13 800
Generic Applications	From €11 600
Approval of a drug in the Decentralized method (DCP)	
With Germany as the Reference Member State (RMS)	
Authorization of medicinal products / new substance	From €89 300
Hybrid Applications	From €37 900
Generic Applications	From €31 800
With Germany as the Member State concerned (CMS)	
Approval of a drug / new substance	From €19 500
Hybrid Applications	From €15 900
Generic Applications	From €13 900
Renewal of authorizations	12 600
Extension of a marketing authorization	
Drugs with new or known substance **(National Procedure)**	€6 200
Extension of a marketing authorization in the (MRP) or in the (DCP)	
With Germany as Reference Member State (RMS)	€9 600
with Germany as Member State Concerned (CMS)	€4 000

https://www.bfarm.de/SharedDocs/Downloads/DE/Service/Gebuehren/AMG-KostV2015.pdf?__blob=publicationFile&v=4