# Germany

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The current situation with regard to drug registration in Germany is the result of a long medical tradition that differs in some respects from that of other European countries. Unlike most European countries, Germany still has a lot of pharmaceutical products on the market with active ingredients on a phytogenic basis. There is a strong belief among patients in the efficacy of herbal remedies, especially to alleviate minor disorders such as coughs and colds, gastrointestinal problems, or sleeplessness.

Another unusual aspect is the continuing important role of homeopathic treatments. Starting with Samuel Hahnemann at the beginning of the nineteenth century, this form of medication involving high dilutions of the active principle still enjoys a strong following, mainly in paramedical circles but also in pediatric and veterinary medicine, particularly for the treatment of chronic diseases where the absence of side effects makes it especially attractive. The philosophy of treating the patient as a complete entity comprising body, spirit and soul was extended by Rudolf Steiner in the 1920s and a whole series of new medicines were developed in response to this holistic concept of health and disease.

"Modern" medicines are also in use, and the Drug Law provides guidance on the conditions under which drugs for all kinds of therapy can be approved for marketing. The regulator's task is to apply the law without mixing the standards for the different categories, since a herbal remedy can never meet the same approval criteria as a chemical entity, and vice versa. A variety of transitional regulations are currently in force to allow the manufacturers of traditional remedies that have been on the market since at least 1976 to adapt their files to modern standards. However, the backlog in reviewing such "legacy drugs" is still enormous because of the difficulty proving efficacy for such traditional remedies. The latest estimate suggests that about 16,000 medicinal products without proven efficacy

are still on the market. The latest deadline for this updating process was the year 2004, although according to European Union (EU) requirements the reregistration procedure should have been completed in 1990.

With the 10th Amendment of the Drug Law, which will come into force presumably in May 2000, the deadline for updating existing registration files with pharmacological, toxicological and clinical data, together with the corresponding expert reports, will be shifted to the end of the year 2000. This Amendment is the reaction of the German Parliament to a letter of complaint from the European Commission, which requested the legislator bring the law more in line with the requirements of the EU.

## COUNTRY DESCRIPTION

Since the reunification of Germany in 1990, only one registration procedure is necessary to gain access to the whole pharmaceutical market, which was worth roughly Deutschemarks 50 billion at 1996 retail prices. This ranks Germany third in the world after the United States and Japan.

Almost 1,200 manufacturers (including self-producing pharmacies) produce 1,728 million drug packs a year (1996), with about 10 percent of the market (in value) consisting of products of herbal origin. Considering the relatively low price of these products, the market share in volume terms is even bigger. The trend towards self-medication has increased as a result of the decision of the health insurance funds to stop automatic reimbursement for medicines to treat minor ailments such as coughs and colds, sleeplessness, and headaches, and for preparations such as sedatives, laxatives, enzyme combinations, geriatrics and vitamin and mineral supplements.

## OVERVIEW OF REGULATORY ENVIRONMENT AND BACKGROUND

With the Drug Law of 1961, Germany—for the first time in its history—introduced modern legislation regulating the medicines industry. This law was amended in 1976 to bring it into line with the guidelines issued by the Commission of the European Economic Community (EEC) requiring the adaptation of national laws to the Treaty of Rome for the creation of a common market.

The German constitution (Grundgesetz) provides that legislation be implemented by the individual states (Länder) unless specifically stated otherwise. The administrative supervision of the manufacture and distribution of medicines and the monitoring of observance of the Drug Law is thus entirely the responsibility of the authorities of that state in which the pharmaceutical enterprise is domiciled. The federal authorities' competence is concentrated in two areas:

- The registration of drugs and their approval for marketing.
- The central recording and evaluation of side effects and the coordination of appropriate safeguards.

Because the granting of marketing authorization (MA) is a federal matter, many other regulations are also applied centrally. They include the following, according to their position in the official law:

- Decree on medicaments sold in pharmacies only or generally
- Decree on prescription-only medicaments
- Decree on the competence of the Paul Ehrlich Institute (PEI)
- Decree on the automatic obligation for prescription
- Decree on the standard approval for finished drugs
- Decree on the standard registration of finished drugs
- Decree on the designation of active ingredients in finished drugs
- Decree on radioactive drugs or medicinal products treated with ionizing rays
- Decree on the ban of using ethylene oxide on herbal remedies
- Decree on warning notes (in case of ethanol and/or tartrazine contained in the medicament)

More than 40 such decrees have been issued so far with periodic revisions so that, in case of uncertainty about a regulation, it is advisable to first check the list of special decrees in order to identify the latest edition.

Besides the Drug Law, there are separate laws on food, tobacco products, cosmetics, and commodity products. Narcotic substances and medical devices are also regulated by a special law.

## REGULATORY AUTHORITIES

Until 1993, the sole authority for registration and marketing approval was the Federal Health Office (Bundesgesundheitsamt or BGA), together with the Paul Ehrlich Institute, with responsibility for sera and vaccines and for test allergens, sera and antigens.

In that year, following revelations that more than 2,000 haemophiliacs had contracted AIDS as a result of being given HIV-infected blood products, the government decided to dissolve the existing organization and reallocate responsibility among four separate organizations reporting directly to the Minister of Health: the Federal Institute for Medicinal Products and Medical Devices (BfArM), the Paul Ehrlich Institute (PEI ), the Federal Institute for Consumer Health Protection and Veterinary Medicine (BgVV), and the Robert Koch Institute for Infectious and Non-infectious Diseases. The principal changes involved the transfer of responsibility for blood products to the PEI, in addition to its previous tasks, and the creation of

the BgVV as a completely new organization with responsibility for the registration and marketing approval of veterinary medicines, as well as other important matters.

The Robert Koch Institute is also responsible for the approval of gene technological procedures, but not for gene therapy.

### Addresses

- Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM)
  (Federal Institute for Medicinal Products and Medical Devices)
  Seestraße 10-11, D 13353 Berlin, Germany
  Phone: 49 030/4548-30
  Fax: 49 030/4548-3207

- Bundesinstitut für gesundheitlichen Verbraucherschutz und Veterinärmedizin
  (Federal Institute for Consumer Health Protection and Veterinary Medicine) (BgVV)
  Thielallee 88-92, D 14195 Berlin, Germany
  Phone: 49 030/8308-0
  Fax: 49 030/8308-2741

- Bundesinstitut für Infektionskrankheiten und nicht übertragbare Krankheiten—Robert Koch-Institut
  (Federal Institute for Infectious and Noninfectious Diseases)
  Nordufer 20, D 13353 Berlin, Germany
  Phone: 49 030/4547-4
  Fax: 49 030 4547-2328

- Bundesamt für Sera und Impfstoffe—Paul Ehrlich-Institut,
  Paul-Ehrlich–Straße, 51–59, D 63225 Langen, Germany
  Phone: 49 06103 770
  Fax: 49 06103 77123

## REGULATORY REQUIREMENTS AND PROCEDURES

As an EU Member State, Germany is bound by the Council Directives of the European Union and is obliged to accept MAs granted under the centralized/biotech and decentralized procedures, which are described elsewhere. This chapter is therefore confined to the description of the national registration process and to strictly national applications for marketing approval. The legal basis for drug registration in Germany is found in sections 4 and 5 of the Drug Law (Arzneimittelgesetz), including the supplementary decrees and the underlying international regulations (EU Directives).

The various steps of the procedure are described as follows.

- For each pharmaceutical dosage form, an application form has to be filled in (these forms are available through the Bundesanzeiger Verlag, Köln ).
- An application can only be filed by a pharmaceutical entrepreneur, which can be the importer of a drug or a distributor.
- The complete application file, together with the application form, is submitted to the Bundesinstitut für Arzneimittel und Medizinprodukte, Fachregistratur, Genthiner Str. 38, 10785 Berlin. (An electronic submission is only possible in case of compatibility with the DAMOS system and only in addition to the paper submission).
- A project number is assigned and communicated to the applicant together with the acknowledgment of receipt for the dossier.
- A pre-check for completeness is made as well as a check to see if the drug has been sufficiently tested pursuant to the presently prevailing standard of scientific knowledge. If data are missing, the applicant must remedy the deficiencies, usually within three months.
- The file is then distributed to the different departments for assessment.

After the review process, which should last no longer than seven months, the authority must decide whether the drug can be approved or not. In contrast to many other countries, the fees have to be paid only after the conclusion of the procedure.

The competent federal higher authority may only refuse the MA if:

- the documents submitted are incomplete;
- the drug has not been sufficiently tested pursuant to the respective prevailing standard of scientific knowledge;
- the drug does not show adequate quality pursuant to the acknowledged pharmaceutical principles;
- the therapeutic efficacy attributed to the drug by the applicant for MA is lacking or is insufficiently substantiated by the respective prevailing standard of scientific knowledge;
- there is reason to suspect that, under correct use, the drug has harmful effects that exceed the bounds considered justifiable in light of current medical knowledge;
    - a sufficient substantiation is lacking that, in a drug containing more than one medically active constituent, every constituent contributes to the positive judgement of the drug, whereby the particulars of the drug concerned have to be considered according to the risk;

- the stated withdrawal period (the period between the last medication and the use of the animal as food) is insufficient;*
    - the given residue test procedure cannot reliably prove the type and amount of substances which are detrimental to health or cannot be carried out as a matter of routine;*
    - in the case of premix drugs, the control method used to prove the quality and quantity of the active constituents in the medicated feeding stuffs cannot be carried out as a matter of routine;*
    - the drug is intended for administration to animals used for the production of food and if the drug contains a pharmacologically active constituent which is not listed in the Appendix I, II or III of Regulation (EEC) No. 2377/90;*

    (* These paragraphs refer exclusively to veterinary drugs.)
- the marketing of the drug would violate legal regulations, an order, or a guideline of the Council or the Commission of the European Communities;
- the drug is exempted from the obligation of authorization by ordinance pursuant to § 36 para 1 or is identical with such a drug in the type of the medically active constituents as well as comparable in regard to their amount unless a justified interest in an authorization pursuant to para 1 for export purposes can be substantiated.

The MA must not be refused pursuant to subpara 4 because therapeutic results have been achieved in a limited number of cases only.

Therapeutic efficacy is lacking unless the applicant furnishes proof according to the presently prevailing standard of scientific knowledge that therapeutic effects can be achieved by the drug.

The MA shall be refused for a drug which is different from a drug bearing the same name authorized for marketing or already on the market due to the nature or quantity of its active constituents. A difference in the quantity of active constituents shall be harmless if the drugs are different in their pharmaceutical form.

In the case of objections raised against the documents submitted, the applicant shall be given the opportunity to correct the faults within an appropriate period of time. Should these faults not be corrected, the MA shall be refused.

The MA shall be granted by virtue of the examination of the documents submitted and on the basis of the expert opinions. For assessment of the documents, the competent federal higher authority may utilize its own scientific results, call in experts or request expert opinions. Furthermore, the competent federal higher authority may have the documents assessed by independent counter-experts and take as a basis their assessment for the decision of the MA. The competent federal higher authority may commission a counter-expert who possesses the necessary

expert knowledge and the reliability necessary to work as a counter-expert. Upon request, the applicant shall be permitted to peruse the expert opinions. If the applicant asks to call in experts selected by himself, these persons shall also be heard. On request of the MA holder or the applicant, the competent federal higher authority issues an evaluation report unless such a report has already been issued by the competent authority of another Member State; the evaluation report will be updated upon request in case new relevant information on the quality, harmlessness or efficacy of the drug in question is available.

If the drug was already approved in another Member State of the EU this approval must be acknowledged on the basis of the evaluation report delivered by this state unless there is a reason to believe approval of the drug may be a hazard for the public health or, in case of a veterinary drug, a hazard for the health of man, animal or the environment. In this exceptional case, the competent federal higher authority must involve the committee for finished drugs or for veterinary drugs.

If an application for registration made after 1 January 1995 is already under examination in another Member State of the EU or if the evaluation report of this state is not yet available, the competent federal higher authority may suspend the approval process until the evaluation report of that Member State is available. An application made after 1 January 1998 has to be suspended if an MA is granted in the other Member State.

The competent federal higher authority shall have the application for the MA examined by independent experts to determine its completeness and whether the drug has been sufficiently tested pursuant to the prevailing standard of scientific knowledge. In case of objections, the expert shall give the applicant the opportunity to remedy the deficiencies within three months.

The competent federal higher authority shall reach its decision on the application for the MA within a period of seven months.

The authority may combine the MA with the imposition of conditions. Conditions may also be imposed subsequently. These mainly concern the labelling of texts on the containers and outer packages as well as the package leaflet.

Any changes occurring in the particulars and documents supplied shall be notified. The applicant has to inform the authority immediately, but no later than 15 days after the case becomes known, of any suspected serious side effect or serious interaction with other products as well as frequent or considerable abuse observed in an individual case if it can directly jeopardize human or animal health. He shall keep a record of suspected cases different from serious side effects or interactions with other products which have come to his knowledge from a member of a medical profession. Unless otherwise imposed by conditions, the applicant shall present these records to the authority immediately upon request or at least every six months during the first two years after the authorization was granted and annually during the next three years. Then, he shall present the documents every five years or immediately upon request along with the application for prolongation of the authorization. All existing documents on the evaluation of suspected cases or of observed abuse as well as a scientific evaluation shall be presented to the authority.

In the case of a change of the name of the drug, the approval letter shall be amended accordingly. A pharmaceutical entrepreneur may place the drug on the market under its former name for a further period of one year, wholesalers and retailers for a further period of two years, beginning on the following 1 January or 1 July after the promulgation of the change in the *Federal Gazette*. Any of the following changes shall be implemented if the authority has given consent:

- The dosage, type or duration of application, new indications within the same therapeutic area as well as in case of a restriction of the contra- indications, side effects or interactions with other products, as far as drugs are concerned which are excluded from distribution outside of pharmacies.
- The pharmaceutically active ingredients excluding the medically active ingredients.
- To a pharmaceutical form comparable to the authorized form.
- Treatment with ionizing radiation.
- The manufacturing or control procedure or the indication of a prolonged shelf life of sera, vaccines, blood products, as well as of gene technological manufacturing procedures.
- The package sizes.

The consent shall only be deemed as granted if no objections to the change have been filed within a period of three months.

A new MA shall be applied for in the following cases:

- When a change in the composition of the pharmaceutically active ingredients either in type or quantity occurs.
- When a change in the pharmaceutical form (except if comparable to the authorized form) occurs.
- When there is an extension of indications.
- With the introduction of gene-technological manufacturing procedures.
- With a reduction of the withdrawal period (for veterinarian products).

An MA shall be withdrawn if it becomes subsequently known that one of the reasons for refusing the MA existed at the time of issuance or has subsequently developed.

The MA shall furthermore be withdrawn or revoked if:

- it turns out that the drug lacks therapeutic efficacy; or
- the therapeutic efficacy has not been sufficiently proven pursuant to the prevailing standard of scientific knowledge.

The therapeutic efficacy is lacking if it is certain that no therapeutic results can be achieved with the drug. Also, the suspension of the MA may be ordered for a limited period of time. The MA shall expire:

- by written renouncement;
- after the completion of a period of five years as from the date of its granting, unless an application for prolongation is filed up to three months prior to the expiry period; or
- if the extension of the MA is refused.

The application for extension shall be supplemented by a report giving details of whether and to what extent the criteria by which the drug is assessed have changed within the previous five years.

In respect of drugs intended for administration to animals serving the production of foodstuffs, the authority may furthermore demand that the report comprises details on experience gained in the residue test procedure.

In the *Federal Gazette* the authority shall promulgate:

- the granting and prolongation of an MA;
- the withdrawal of an MA;
- the revocation of an MA;
- the suspension of an MA;
- the expiration of an MA;
- the change in the name; and
- the withdrawal or revocation of the release of a batch.

**Registration of Homoeopathic Drugs**

Finished drugs may only be placed on the market as homoeopathic drugs if they have been entered in the Register for homoeopathic drugs kept by the authority (registration). An MA shall not be necessary. A registration shall not be necessary for drugs which are marketed by a pharmaceutical entrepreneur in amounts up to 1,000 packs per year.

The particulars, documents and expert opinions as specified for normal drugs shall be enclosed with the application for registration. This shall not apply to the particulars on the effects and fields of application as well as to the documents and expert opinions on the pharmacological-toxicological tests and clinical trials. The authority shall register the homoeopathic drug and assign the registration number to the applicant in writing. The registration shall only be valid for the homoeopathic drug and its degrees of dilution as specified in the notice of registration. The authority may connect the registration notice with the imposition of conditions. Conditions may also be imposed subsequently.

The authority shall refuse the registration if:

- the documents submitted are incomplete;
- the drug has not sufficiently been tested analytically in compliance with the respective prevailing standard of scientific knowledge;
- the drug does not possess the adequate quality in keeping with the acknowledged pharmaceutical principles;
- there is reason to suspect that, in case of correct use, the drug has harmful effects which exceed the bounds considered justifiable in light of knowledge available of medical science;
- the drug is intended for the administration to animals serving the production of food;
- the withdrawal period given is insufficient;
- the drug, as far as it is intended for the administration to humans, is intended for oral administration and external use;
- the drug is subject to prescription;
- the drug is not manufactured according to a procedure described in the homoeopathic section of the *Pharmacopoeia*;
- the application as a homoeopathic or anthroposophic drug is not generally known;
- an MA has been granted for the drug; and
- the marketing of the drug or its use in animals would violate legal regulations.

If the drug has already been registered in another Member State of the European Communities or in another contracting state of the Agreement on the European Market, the registration shall be granted on the basis of this decision unless there is a reason for refusing as previously defined.

The registration shall expire at the termination of a period of five years following its grant unless an application for prolongation has been made three to six months before expiration.

The Federal Ministry shall be empowered to issue provisions by decree, subject to the consent of the Federal Council, on the obligation of notification, on renewed registration, cancellation, costs, promulgation and exemption from registration of homoeopathic drugs in compliance with the provisions on an MA. The decree shall be issued in agreement with the Federal Ministry of Food, Agriculture and Forestry as far as drugs intended for administration to animals are concerned.

Proof of efficacy is not required for homeopathic preparations as long as no claims are made regarding efficacy in specific indications.

### Approval of Medicinal Products with Active Substances of Vegetable Origin

The procedure for approval of medicinal products with active substances of vegetable origin is basically the same as for products with chemically synthesized active substances. However, there are a number of special features of plant–derived substances that may lead to less strict application of the normal approval criteria.

For example, such substances often have a characteristic taste that makes it impossible to test them in double-blind trials. Proof of efficacy therefore has to rely on alternative methods, such as testing in individual patients. Standard clinical testing is not always possible either, because the majority of such products are only intended to be used to treat fairly mild disorders under ambulant conditions.

Preparations of vegetable origin are frequently traditional remedies used in popular medicine. In most cases they are a mixture of several different active constituents, making it more difficult to elucidate their precise pharmacological and toxicological properties. It also means that isolation of their active principles in order to achieve content uniformity of the individual dose units is the exception rather than the rule.

Efforts to standardize the evaluation and approval criteria for medicinal products of vegetable origin led to the appointment of a committee with a brief to produce monographs on the basis of the available literature. The workload of this committee proved particularly heavy on account of the large number of plant-derived medicines in use as popular remedies. This problem was compounded by the fact that many of them are used to treat several different conditions, although only conditions for which there was literature-based evidence were included in the monographs. This means that evidence of efficacy in the form of proven uses has to be provided to support any claim not covered by the relevant monograph; in the case of combination preparations, evidence has to be submitted showing the contribution to overall efficacy of each individual constituent. Similar work has now been started at the international level, for example the European Scientific Cooperative on Phytotherapy (ESCOP) monographs.

## FUTURE TRENDS

For larger companies, the European centralised/multistate procedure will be the only option in order to penetrate the markets with new products as quickly as possible. The fees for this procedure are very high, which is a deterrent to smaller companies since this procedure would be a major investment for them with a small chance of a successful outcome. The procedure is complicated and very formal, which makes it difficult for small companies to cope with the requirements. Thus the national registration procedure remains an attractive alternative for smaller companies since the market size is still big enough, even for products with a modest degree of innovation.

The strong tendency towards phytotherapy and self-medication is further supported by health insurance companies which exclude medication for minor diseases from the list of reimbursed products. So-called lifestyle drugs and functional food are the industry's reaction towards such trends. Patients take care of their health in a more responsible manner and try to prevent severe and chronic diseases by changing their lifestyle and controlling their food intake. Dietary measures instead of medicine represent the new approach toward a healthier life. A profound distrust of genetically engineered food has paved the way to a "back to nature" trend with a preference for products with the "bio" label.

The regulatory field will be dominated by a few larger companies with their own research and development which generate highly innovative products with a patent protection enabling sufficient return on R & D investment. For medium-sized and small companies, the application of new technologies to already existing drugs or labelling extensions will be the main sphere of activities.

In order to avoid the time-consuming and expensive registration procedures, the activities will be directed to the invention of so-called nutraceuticals, a nutrition with intended "pharmacological" effects. However, the legal basis for such products is relatively small, compared to that in other countries such as the United States or Japan.

## ABOUT THE AUTHOR

Dieter K. Zeppenfeldt, a registered pharmacist, worked for two years in a community pharmacy in Cologne followed by a 2-year period of national service at the German army's Institute for Defence Pharmacy and Food Chemistry. He then joined SANDOZ AG's R & D division. He was initially responsible for developing technical documents and later worked in the Drug Registration and Regulatory Affairs department of the marketing division for 18 years. His activities included country support, project work, computer-based organizational tasks and coordination of registration activities for newly developed products. Mr. Zeppenfeldt was later responsible for registration in the countries outside the EU without their own R & D division. He currently is a consultant in regulatory questions regarding foodstuffs and drugs.