SUSTAINABLE ACCESS TO MEDICINES IN EUROPE

Priorities for a Modern EU Health Policy
The Bundesverband der Arzneimittel-Hersteller (BAH), the German Medicines Manufacturers’ Association, represents the interests of the pharmaceutical industry in Germany, and is comprised of global companies as well as local small and medium enterprises (SME). By company membership BAH, with its over 450 members, is the leading trade organisation of the pharmaceutical industry in Germany. BAH members create about 80,000 jobs in Germany. BAH caters for the entire range of the industrial landscape, from self-medication medicines (‘OTC’) through to prescription drugs (‘Rx’) and medical devices. BAH advocates for safe and responsible self-medication through professional medical and pharmaceutical advice. Therefore, BAH strongly supports the statutory protection of the owner-operated pharmacy as the primary institution for distribution. BAH is a competent, reliable and trustworthy partner for the federal government, politicians, authorities and institutions in health policy and constitutes a strong link between the different stakeholders.

At European level, BAH is represented through its Brussels-based umbrella organization the ‘Association of the Self-Medication Industry’ (AESGP). AESGP represents the interests of its members in front of the European institutions and other relevant organisations and stakeholders.
FOREWORD

Brussels, Strasbourg and London – Europe is of great importance for Germany’s largest trade association of the industry, the ‘German Medicines Manufacturers’ Association’ (BAH). Through our European umbrella organization, the ‘Association of the European Self-Medication Industry’ (AESGP), we are right in the heart of the European quarter in Brussels, and maintain close contacts to European institutions and the numerous different organizations on site. As part of our enhanced commitment to European politics, BAH has compiled this new publication entitled ‘Sustainable Access to Medicines in Europe – Priorities for a Modern EU Health Policy’.

The European system for marketing authorisation of medicinal products, harmonised provisions for pharmacovigilance, the single European market, as well as free movement of persons in Europe, are important factors from which the pharmaceutical industry has already gained benefits for many years. They have also significantly improved the access of patients to medicines in Europe. Europe will continue to assume its role of a pioneer in innovation as well as quality and safety of medicines.

The present publication describes the broad spectrum of topics in which BAH engages at the European level: from the Brexit to the new EU ‘Medical Device Regulation’ (MDR) and the European ‘Health Technology Assessment’ cooperation (HTA), from the EU Falsified Medicines Directive to health claims and the EU Regulation on clinical studies.

The engagement of BAH at European level is multifaceted. In times of crisis in Europe, the pharmaceutical industry feels even more committed to the European idea – and this publication should be understood in this sense. I would be pleased if this publication is of interest and serves as a useful basis for further discussion.

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German ‘Mittelstand’ in Europe

STRENGTHEN SMALL AND MEDIUM-SIZED ENTERPRISES

Small and medium-sized enterprises (SMEs): they develop, produce and market prescription only and non-prescription medicines which are important for health care. The so-called SMEs are facing increasing administrative regulations and increasing pricing pressure. This has an immediate impact on their competitiveness.

According to the German Institute for Research on Small and Medium-sized Enterprises (Institut für Mittelstandsforschung, IfM) based in Bonn, SME are defined as enterprises with a staff of less than 500 people and an annual turnover of up to EUR 50 million. In 2015, the entire staff of the 342 German pharmaceutical manufacturers amounted to 114,000 people. About 85 percent of these companies are classified as SME, based on the size of their staff.

Due to increasing regulatory requirements and growing pricing pressure induced by legal reimbursement regulations, small and medium-sized pharmaceutical enterprises are facing particularly enormous challenges. At the same time, it is just this sector which is often considered to be the ‘economic locomotive’ of Germany. Over 99 percent of all German enterprises are characterized as medium-sized. Among the members of the BAH the percentage is 84. The total number of SMEs in Europe is about 23 million, of which about 3.7 million are based in Germany. Their contribution to the pan-European economic performance amounts to about 60 percent.

The economic locomotive should not be slowed down...

German small and medium-sized pharmaceutical enterprises have been a successful and integrative component of the German health system for decades, with many for more than a century. The companies create professional and sustainable jobs and are situated in rural as well as in urban regions. Many pharmaceutical SMEs possess strong regional roots and have been family managed for generations. This not only shapes their corporate culture, but is of utmost importance for the regional economy. Personal corporate management and continuous business contacts are the most important guarantees for solid growth and to ensure the supply of patients.

SMEs are in no way inferior to large companies: The number of SMEs and larger companies engaging in research and development is almost equal. This has been demonstrated by a member survey undertaken by BAH. SMEs invest in the future: The rate at which SME members of BAH offer professional training almost equals the rate of large-scale enterprises, with focus on commercial, natural science, technical and IT educations. The rate is higher by far than the German average.

…but rather be kept under steam

With a view to the importance of SMEs as an economic factor, more attention should be dedicated to their specific concerns on the European level, and adequately designed legal rules should reduce the burden on them to keep them innovative. This is necessary because, due to their structure and history, these enterprises are an important motor for economic development. SMEs could for example be supported by funding and investment programmes like the EU Framework Programme for Research and Innovation ‘Horizon 2020’.

With a view to their economic impact for Germany, it is important to protect small and medium-sized pharmaceutical enterprises from consistently increasing administrative barriers.
Constructive integration of SMEs in Horizon 2020 means: The companies should be granted simple and fast access to subsidies and the use of the Enterprise Europe Network (EEN) as a central contact point. Besides an improved framework for investments, the initiative envisages establishing a European Fund for Strategic Investments (EFSI). This EUR 21 billion fund will mobilise funds from the private sector for strategic investment projects and consequently promote innovative projects in the area of research and development. The initiative will open up specific opportunities for small and medium-sized enterprises, secure jobs, create new jobs and generate innovative products. Following the principle of ‘boosting strengths’, the European Commission should furthermore intensify the promotion of exports, with the aim to expand the export competence of German small and medium-sized pharmaceutical enterprises. Through trade promotion the European Commission should further support small and medium-sized pharmaceutical companies by suitable market information or networks, complementary to international trade agreements.
LESS IS MORE

To evaluate European law-making and to reduce restrictive rules to the necessary minimum are the objectives of the initiative ‘Better Regulation’ which has been adopted by the European Commission. Better Regulation means: less quantity, more quality – achieved by more transparent decision-making processes and improved impact assessment.

The European Commission intends to evaluate existing law in terms of its up-to-dateness and efficacy by the ‘Regulatory Fitness and Performance Programme’ (REFIT). In order to increase transparency and quality in future European law-making processes, the Better Regulation initiative places special focus on the impact assessment by the European Commission as well as consultation processes with stakeholders, i.e. relevant players of the society and economy.

**Increased quality and acceptance by involvement of stakeholders**

Systematic involvement of stakeholders ensures that the broad expertise of all concerned players is taken into account. Furthermore, it leads to smoother implementation and a higher degree of acceptance. The more detailed the input from stakeholders, the more tailored the impact assessment of law-making initiatives. Active involvement of stakeholders in the decision-making process may contribute to higher quality of results, reduced costs and reduced workload on the European Commission. Therefore, the Better Regulation initiative belongs to the priorities of the European Commission.

**Reduce burden on small and medium-sized pharmaceutical manufacturers**

Small and medium-sized enterprises suffer particularly from the consequences of legislative over- and misregulation. They normally have the least resources to cope with regulatory requirements. Hence, these companies may benefit to a great extent from the efforts of the European Commission.

As the pharmaceutical sector is strongly regulated, better law-making in this area could especially produce returns for this industry. Consequently, the trend of imposing more and more regulatory requirements on pharmaceutical manufacturers in recent years could be halted. European legislation should focus on the necessary protection of patients and consumers and ensure that no further hurdles emerge which might jeopardize the access of patients to medicines. Together with its European umbrella association AESGP (‘Association of the European Self-Medication Industry’), BAH will continue to argue for well-balanced and efficient European legislation.

Better Regulation: Strengthening stakeholder involvement in the European Union
Global export of German medicines still continues to be hampered by trade barriers. The European Union strives to remove these obstacles largely by Free Trade Agreements with many countries and regions. A prudent European trade policy can support pharmaceutical manufacturers in making optimal use of their potential.

Trade and investments are the basis for economic growth and employment: In 2016, German pharmaceutical manufacturers exported medicinal products worth EUR 70 billion to all parts of the world. In the same year, German pharmaceutical manufacturers gave jobs to about 116,000 people. Since 2010, this number has grown by 13 percent which is above the average.

Trade policy belongs to the competences of the EU. According the Treaty on the Functioning of the European Union (TFEU), the European Commission conducts trade policy together with the EU Member States and ‘shall contribute […] to the harmonious development of world trade, the progressive abolition of restrictions on international trade and […] the lowering of customs […]’.

**Trade barriers for medicinal products**

The European Commission has managed to reduce tariff and non-tariff barriers to trade and to achieve better access to markets. Notably, non-tariff barriers to trade are major obstacles for pharmaceutical companies. The term means barriers to foreign trade other than tariffs, levies or export subsidies. It comprises predominantly costly and time-consuming marketing and registration procedures which German pharmaceutical companies have to pass in different countries as well as, for example, unnecessary costs for multiple inspections of manufacturing plants. These financial consequences particularly affect small and medium-sized enterprises.

To harmonize rules and standards and to avoid double work are the key objectives of free trade agreements. Pharmaceutical manufacturers place great hopes on the transatlantic free trade agreements between the EU and Canada (Comprehensive Economic and Trade Agreement, CETA) and between the EU and the United States (Transatlantic Trade and Investment Partnership, TTIP).

TTIP, for example, includes mutual recognition of inspection reports.

Another proposal of the European Commission in the framework of TTIP relates to the mutual recognition of EU and US-marketing authorisations for generic medicines and biosimilars. Generics, often called ‘me-toos’, are medicinal products which are launched to the market after expiry of the patent protection of the originator. Biosimilar medicinal products are manufactured with biotechnological procedures. They are placed on the market as follow-up of biopharmaceutical products which are no longer under patent protection.

It remains to be seen whether the current US government will pursue TTIP further. Irrespective of this question, the Food and Drug Administration (FDA), the competent authority for market approvals of medicinal products in the USA, is already cooperating with its European counterpart EMA to achieve a mutual recognition of GMP-inspections (GMP – ‘Good Manufacturing Practice’).

The reduction of global trade barriers and the harmonisation of regulatory requirements should continue to lead global trade policy. This should, however, not lower existing standards on the EU level. The high level of quality, safety and efficacy of medicinal products should be maintained – for the benefit of patients.

To ensure that pharmaceutical manufacturers can make maximum use of their potential, harmonization of international standards is essential.
MAINTAINING MARKET ACCESS

The decision of Great Britain to leave the European Union (EU), the so-called ‘Brexit’, will have far-reaching consequences for the European economy and especially for German pharmaceutical manufacturers. These consequences will be economic and regulatory. The ultimate ambition should be that access to the British market is maintained.

Following the decision of the British citizens of 23 June 2016 in favor of Brexit, the EU will lose the second largest national economy of Europe behind Germany. Pursuant to European law, the negotiations setting out the arrangements for the withdrawal must be completed within a maximum of two years, but prolongation of the deadline is possible. The parties expect far longer negotiations, with a few even up to ten years.

Economic and regulatory consequences

Withdrawal of Great Britain from the European common market would have negative economic consequences for pharmaceutical manufacturers: In the simplest case as trade delays, in the extreme case as export losses. In 2015, German pharmaceutical manufacturers exported pharmaceuticals worth more than EUR 7 billion to Great Britain. Pharmaceutical goods worth about EUR 1.5 billion went in the opposite direction. German manufacturers would especially feel the effects of a loss of the British market.

Brexit would also have an impact on the regulatory sector. The ‘European Medicines Agency’ (EMA) which is (still) based in London is in charge of the centralised European marketing authorization procedure for medicinal products. After Brexit, Great Britain will be excluded from ordinary participation in this procedure. In addition, the EMA will have to move to an alternative location in the EU.

Recognition of existing marketing authorisations

Great Britain must now immediately create national rules for the recognition of centralised marketing authorisations of medicinal products. The approval of new medicinal products will have to be based on national procedures conducted by the British competent Authority, the ‘Medicines and Healthcare Products Regulatory Agency’ (MHRA). This new environment might diminish the attractiveness of the British pharmaceutical market for European pharmaceutical manufacturers. British companies must also be prepared for consequences in other ‘European’ areas. Besides marketing authorization of medicines, this applies to clinical studies and pharmacovigilance as well as funding of research and the European collaboration concerning the assessment of the effectiveness of medicinal products, the so-called ‘European Network for Health Technology Assessment’ (EUnetHTA).

In principle, existing centralised European marketing authorisations of medicinal products, as well as those granted in decentralised procedures, should remain valid and be recognized by Great Britain without any restrictions. Only by this approach can the British market be maintained for European pharmaceutical manufacturers and access to medicines for patients be ensured.

Great Britain plays an important role as reference or concerned Member State in European marketing authorisation procedures. Presumably several thousand existing marketing authorisations will now have to be transferred to other national competent authorities. New rules will have to be established for the participation of Great Britain in European marketing authorization procedures for new medicines. An impairment of the excellent function of the European marketing authorization system or assurance of the safety of medicines would not be acceptable under any circumstances.
Self-medication with non-prescription medicinal products

EMPOWERS PATIENTS, RELIEVES PRESSURE ON SOCIAL SYSTEMS

Self-medication as the treatment with non-prescription medicinal products (over the counter – OTC medicines) under personal responsibility – or after consultation of a pharmacist or physician – is an essential element of health care. From an economic viewpoint, self-medication reduces the pressure on social security systems, e.g. because OTC products must normally be paid for by the patients/consumers and costs for the consultation of a physician can be reduced.

Besides the above, self-medication has medical and social importance and is crucial for health policy: Non-prescription medicines are extremely safe and easy to access in pharmacies. In addition, if consultation of a medical practitioner is substituted by self-medication, the saved resources can be spent for serious diseases. Self-medication is suitable for the treatment of minor diseases, the adjuvant treatment of chronic diseases as well as for the prevention of minor diseases.

OTC medicines in a narrow sense are those medicines which are restricted to pharmacies, but in a broader sense include medicines which can be bought outside pharmacies, as well as health products which can be sold in or outside pharmacies.

Self-medication stands for the involvement of the patient in the healing process. In pharmacies, the consumers can get professional advice from health care practitioners who take their individual situation into account. This may increase acceptance of therapy by the patients as well as safety of use and efficiency of care. This established and well-operating system should be preserved and the pharmacy-only principle be strengthened.

Promotion of self-medication

How can the framework for self-medication be improved and, by this, self-medication be further promoted?

One option would be more positive incentives for pharmaceutical manufacturers to initiate so-called ‘switches’. Switch means the procedure for the change of the classification for the supply of a medicinal product from prescription-only to non-prescription status. More transparency in the switch-procedure could be such an incentive. More switches could create more opportunities for patients to procure medicines quickly, but in a quality-assured manner via the advice provided in pharmacies.

Furthermore, patients need comprehensive information on the efficacy, safety and correct use of non-prescription medicines. Communication training or health education for and with pharmacists could contribute to this.

Together with its European umbrella organization, the ‘Association of the European Self-Medication Industry’ (AESGP), BAH is committed to a strong position of self-medication with non-prescription medicines and an adequate design of the regulatory surroundings.

High market share of non-prescription medicines

Self-medication is of great economic importance: In Germany, 741 million packages of non-prescription medicines were sold in pharmacies in 2016, more than every second dispensed package. Traditionally, the German market of non-prescription medicines offers a broad range of therapeutic options. It includes chemically defined products as well as the so-called ‘special therapeutic disciplines’ comprising herbal, homoeopathic and anthroposophic medicines. In 2016, the share of these products amounted to about 31 percent of the total turnover of non-prescription medicines.

The safe use of medicines in self-medication is to a high degree ensured by the expertise of pharmacists as health care practitioners.
National competences in the EU

SUBSIDIARITY AND EUROPE ARE NO CONTRADICTION

The principle of subsidiarity in public health in the EU stipulating that every Member State organises health care of its citizens by itself and common action via EU institutions are no contradiction. Moreover, they complement each other in a reasonable way with the aim to ensure comprehensive, sustainable and at the same time economic health care in Europe.

Because of the diverging national health systems in Europe, the EU has with good reason agreed on the principle of subsidiarity in the Treaty of Amsterdam. According to this principle, the EU ensures a high level of health protection and combats cross-border threats to health, whereas the Member States are responsible for the organisation of their national health systems and the delivery of medical care for their populations.

The EU ensures comprehensive protection of health

One example of the importance of the EU for the promotion of public health is the establishment of the ‘European Medicines Agency’ (EMA). It is justly considered a big landmark in the development of public health in Europe. The European ‘Health Technology Assessment’ (HTA) process could emerge as a further landmark for the assessment of the effectiveness of new medicinal products.

In addition, the EU may further contribute to the sustainable and economical supply of medicines. It can and should create an innovation and competition friendly climate in which the manufacturers of innovative products, biotechnological medicines (so-called biologics or biosimilars), generics and herbal medicines strive for individually tailored and comprehensive care for patients. The greater the variety of medicinal products, the more intense competition for best care will be.

Member States must take national particularities into account

The Member States of the EU pursue divergent approaches to pricing, models for rebates and discounts and for the reimbursement of health services. Average net incomes as well as purchasing power parities also differ to a great extent. Furthermore, the supply structures as well as financing and assessment of health services have historically developed in different directions. With this background, a sound comparison of the prices of medicinal products in Europe is neither possible nor deemed politically desirable. Attempts to create comparability of the prices of medicinal products via European price data bases, as for example EURIPID, are not promising and negate economic reality in Europe.

The value of medicinal products is multidimensional. For the constitution of reimbursement prices, different costs of hospitalisations, chronifications and work losses should be taken into account. This can however only be achieved close to market and tailored to the individual patient. It further requires adequate consideration of the surroundings in terms of social security systems and economic framework conditions in the respective country.

Future-oriented health care in Europe will not work without robust pharmaceutical manufacturers committed to innovation and investment. Only those manufacturers which are economically successful can achieve improvements of therapy for the benefit of patients.

Bringing this to success requires reasonable work sharing of the Member States and the EU with its respective competences.
Manufacturers who want to place innovative medicines on the market must provide evidence for their therapeutic benefit. In the EU, this assessment is performed by national organisations via so-called ‘HTA-procedures’ (Health Technology Assessment). The designs of the studies, which are necessary for the assessment, cannot always fulfil the different national requirements. It is the task of the ‘European Network for Health Technology Assessment’ (EUnetHTA) to establish standards which serve as the basis for the national decision of each Member State – following the slogan ‘Evidence is global, decision is local’.

‘HTA’ is defined as the systematic, evidence-based assessment of medical procedures and technologies, relating to their impact on the health of the individual, the system and society. Until now this assessment has been performed nationally or even regionally. This is supposed to change: The objective of HTA cooperation is development of uniform European rules for the assessment of the additional therapeutic benefit of medicines – similar to the approach of the European marketing authorization system and pharmacovigilance. This shall be implemented via the common platform ‘EUnetHTA’. EUnetHTA is an independent scientific network of the different European HTA organisations, which is promoted by the European Commission. The aim is to elaborate efficient HTA practices as well as common rules and methods, and by this provide a benefit to the different national health systems. In the end, EUnetHTA will produce ‘joint reports’ which may serve as a basis for the decision of each EU Member State.

Diverging national rules as obstacles

Due to the continuing existence of diverging national and regional requirements, it is not an easy task for pharmaceutical manufacturers to prove the benefit of new medicinal products according to rules everywhere. For example, the starting point and duration of the HTA process, as well as the clinical requirements, differ among the Member States. These diverse national approaches lead to different results of the HTA process, and last but not least to increased workload and costs for pharmaceutical manufacturers. Therefore, they would gain an immense benefit from a uniform European HTA process.

Pursue European objectives

Not only pharmaceutical manufacturers, but also national organisations performing the assessments, profit from consequent implementation of the European HTA process: the first mentioned via uniform rules for efficient proof of the therapeutic benefit of new medicinal products, the latter via uniform assessment criteria and efficient use of resources. This is what BAH together with the ‘Association of the European Self-Medication Industry’ (AESGP) are struggling for. It is deemed important to pursue the objectives of the European HTA cooperation past the expiry of the final funding period of the European Commission in 2020. Until then, BAH together with its member companies and all involved organisations will contribute to further development of EUnetHTA.
The permanent changes to European law on medicinal products are a big challenge for pharmaceutical manufacturers. They include legal and procedural provisions concerning pharmacovigilance, i.e. the safety of medicines, or the harmonization of the requirements of the EU Member States concerning market approval or manufacture, all by themselves welcome objectives. However, the necessary efforts to implement them often outweigh their additional benefit.

Example pharmacovigilance

The most recent revisions of European law on medicinal products related among other areas to pharmacovigilance. However, pharmacovigilance standards in Europe – similar to other sectors of regulation – are already very high. For many stakeholders, further measures require additional efforts including high expenditures of time and money without a perceptible improvement to the safety of medicines. Until several years ago, a risk management plan for medicinal products was only required in exceptional cases. This was changed by the so-called "pharmacovigilance package" of 2010 which also defined the respective regulatory framework conditions. Nowadays, such a plan must be submitted with every application for a marketing authorisation. This even applies
to medicinal products with known active substances for which numerous marketing authorisations have already been granted and for which competent authorities have already acknowledged an unremarkable risk profile and so far never required a risk management plan.

The pharmacovigilance package has also placed immediate financial burden on pharmaceutical manufacturers. New pharmacovigilance tasks for the ‘European Medicines Agency’ (EMA), the competent authority for market approval of medicinal products in the EU, need to be financed. These tasks include the conduct of EU-wide pharmacovigilance procedures, the evaluation of safety-relevant information from scientific literature, scientific assessments and comprehensive information for the public. They are financed by fees paid by the marketing authorization holders. The fees cover pharmacovigilance activities at the EU level, especially those related to EU-wide assessment procedures such as ‘Post Authorisation Safety Studies’ (PASS), ‘Periodic Safety Update Reports’ (PSUR) and risk assessments. In addition, all marketing authorisation holders must pay an annual fee.

BAH believes that these fees are inappropriate. Particularly for marketing authorisation holders possessing a large product portfolio or products with a low market share, the fee structure is problematic. In the midterm, such high pharmacovigilance fees could lead to the effect that even products with significant benefit for patients are no longer marketed and accessible to medical practitioners and patients.

**Example marketing authorisations**

The simplification of procedures for obtaining and maintaining marketing authorisations can be particularly difficult to implement. One example being the ‘better regulation’ initiative of the European system for variations to marketing authorisations. Since 2012 all variations to marketing authorisations in Europe must be submitted to competent authorities according to a uniform system, regardless of whether the marketing authorization has been granted via a European or purely national procedure. Implementation of the system in practice is highly complex and susceptible to errors, and constitutes an enormous workload for marketing authorisation holders and representatives from competent authorities.

**Example GMP**

The requirements concerning Good Manufacturing Practice (GMP) for the manufacture of medicinal products have risen continuously for many years. The increasing complexity of very detailed rules lead to time- and cost-intensive implementing activities, raising the bar especially for small and medium-size enterprises. In the meantime, as well as the actual manufacture of medicines, the manufacture of active substances and other starting materials including excipients and packaging materials, as well as their distribution channels, have been widely regulated. The respective so-called GMP and GDP rules (Good Distribution Practice) have almost doubled during the last decade. This does not only create additional expenditures of time and personnel for the manufacture and testing of medicinal products, the increasing amount of tests and certificates also makes the manufacture of medicinal products more and more expensive.

**Further improvements must be proportionate**

Medicinal products which may be placed on the European market according to European law fulfil high safety standards. The requirements concerning manufacture and marketing authorisation are enormous. This high level is the result of step-by-step adaptation of the European law for medicinal products to technical and scientific progress. Future changes must be proportionate. They should not rely exclusively on theoretical improvements, but must also have a benefit for the patient. On this basis it must be thoroughly evaluated how much effort can be expected from all parties involved, if the objective is not the improvement of a result but ‘merely’ the design of procedural aspects.

"Future changes to the European law on medicinal products must be appropriate. They should not rely exclusively on theoretical improvements, neglecting the necessary resources for their implementation."
Pharmaceuticals in the environment

INDUSTRY LAUNCHES INITIATIVE

Different authorities increasingly perceive the pollution of water and soil with small residues of medicinal products as an emerging environmental problem. In order to improve environmental safety of pharmaceutical substances, pharmaceutical manufacturers have launched an inter-association initiative. Taking environmental issues into account is important. It must, however, not impede the access of patients to medicines.

According to a corresponding EU directive, the European Commission shall present proposals for the reduction of the release of pharmaceutical substances in the environment until 14 September 2017. The proposals will be based on a study commissioned by the Commission. The study results are described in ‘Bio IS Report – Study on the environmental risks of medicinal products’ which was presented at the end of 2013 and also includes potential solutions. So far, the European Commission has not yet deduced any concrete measures from the study and published them.

Associations launched an initiative in Europe

Taking their own responsibility for faster development of approaches to the solution of the issue, the pharmaceutical industry has founded the ‘Inter-Association Initiative on Pharmaceuticals in the Environment’ (IAI PIE). The partners of the initiative are the European pharmaceutical associations – the Association of the European Self-Medication Industry (AESGP), the European Federation of Pharmaceutical Industries and Associations (EFPIA) and ‘Medicines for Europe’.

Based on the BIO IS Report IAI PIE has developed the so-called ‘Eco-Pharmaco-Stewardship (EPS) concept’. It considers the whole life-span of a medicinal product and deals with the tasks and responsibilities of all parties involved, including public institutions, pharmaceutical manufacturers, environmental experts, physicians, pharmacists and patients.

The EPS concept comprises three pillars: Pillar 1 – Research and development/intelligence led assessment of pharmaceuticals in the environment; Pillar 2 – Manufacturing; effluent management; Pillar 3 – extended environmental risk assessment. All three pillars have the aim of gaining new information on the environmental safety of pharmaceuticals, consequently improving appraisal of the issue and reducing emissions of pharmaceuticals in the environment. In addition, the IAI PIE and other organisations have initiated the so-called ‘MEDSdisposal campaign’ (www.medsdisposal.eu) which shall raise awareness on how to dispose of unused or expired medicines appropriately in Europe.

Patient care first

Any discussion about the reduction of residues of pharmaceutical substances in the environment should not neglect the medical supply of patients. When taking a decision on the market approval or use of a medicinal product the benefit of the product for the patient should always have the highest priority. This is the only way to ensure good and sustainable patient care.
Counterfeit protection of medicinal products

SAFETY IN THE PHARMACEUTICAL MARKET

Falsified medicinal products nowadays present a significant threat to public health. In addition, they cause severe economic damage. The EU has reacted to this: Starting 9 February 2019, prescription-only medicinal products may only be released for sale or distribution in the Member States if they bear specific safety features. In Germany, counterfeit protection is implemented by the verification system securPharm.

Counterfeit medicinal products cannot guarantee their efficacy and can damage a patient’s health. But not only health is damaged. The economic consequences of such illegal practices are also severe: A study conducted by the European Union Intellectual Property Office (EUIPO) has revealed that between 2008 and 2013 pharmaceutical manufacturers and wholesalers lost approximately EUR 10 billion of revenue annually due to the presence of counterfeit medicines in the EU marketplace. According to EUIPO these lost sales translate into direct employment losses of approximately 38,000 jobs. As a countermeasure the EU adopted a directive against falsified medicines in 2011. The Commission’s Delegated Regulation which was published on 9 February 2016 provides further details. The safety features on the packages of medicinal products which are defined in the regulation must be implemented within three years after publication of the regulation in the Official Journal. The Delegated Regulation also lays down rules for the establishment, management and accessibility of the repositories system.

In Germany, securPharm does it

securPharm is a joint initiative of BAH, other associations of the pharmaceutical industry, pharmaceutical wholesalers and pharmacists. Since the publication of the falsified medicines directive, this initiative has been working on the implementation of the new rules. The aim is to prevent the entry of falsified medicinal products into the legal supply chain in Germany. For this purpose, securPharm has developed a system that ensures that the authenticity and identity of a medicinal product can be verified in pharmacies before dispensing the package to the patient. Verification is performed with the aid of the safety features that have been placed on the packaging by the pharmaceutical manufacturers. The safety features also allow verification where the packaging of a medicinal product has been tampered with. The Delegated Regulation also includes derogations from the obligation. They apply to: medicinal products subject to prescription which are exempted from the obligation to bear the safety features (‘white list’), medicinal products not subject to prescription which as an exemption must bear the safety features (‘black list’).

All EU Members must go along with it

For comprehensive implementation of the EU falsified medicines directive it is important that stakeholders in other Member States also establish national verification systems, so that a EU-wide system for the verification of the authenticity of medicinal products including the connection with the EU-hub can be assured by 9 February 2019. Verification testing is then performed by the pharmacist via the check of the serial number and the product code on the packaging against the national repository. According to a representative survey of the Health Monitor of the BAH about half of the patients have great or very great confidence in the safety of prescription medicines, this sharing may distinctly increase with the implementation of the falsified medicines directive.
European Medical Device Regulation

PRAGMATIC IMPLEMENTATION FOR SUBSTANCE-BASED MEDICAL DEVICES NEEDED

With the start of application of the Medical Device Regulation (MDR) in 2020, the regulatory requirements for medical devices will increase. Among others, this applies also to manufacturers who want to bring substance-based medical devices to market. Notably, the necessary certification by Notified Bodies might emerge as a problem.

Examples for substance-based medical devices include drops for the treatment of dry eyes, nose sprays based on seawater, laxatives, products for bloating and gastrointestinal pain, various gels, creams and ointments. In contrast to medicinal products, substance-based medical devices do not achieve their intended purpose by a pharmacological, immunological or metabolic mode of action. The new Medical Device Regulation is the result of a long law-making process which was kicked-off in 2012. It will be immediately applicable in all EU Member States. Implementation into national law is not necessary. Consequently, the law will become far more extensive and more than before be dominated by European rules. Not only will regulatory density increase, but the character of rules will also change. Substance-based medical devices will have to face multiple tightenings of rules.
Higher standards impede market access

At the moment many substance-based medicinal products fall under the lowest risk class, i.e. class I. This means that marketing of these products lies within the responsibility of the manufacturer, without involvement of any further institution, however subject to supervision by competent authorities.

In the future, risk class I will no longer be possible for substance-based medical devices. As a consequence, products such as wheelchairs, bandages or walkers will continue to exist as class I medical devices, whereas seawater nose sprays or lozenges with Iceland moss can no longer be brought to market with this legal status. Classification of the substance-based medical devices in question as risk class IIa and higher is associated with a distinct increase in the requirements for marketability of these products, as involvement of a notified body will be obligatory. From the viewpoint of the BAH this might emerge as a problem: On the one hand, the number of notified bodies has markedly decreased during recent years, and a further decrease is to be expected with a view to the modified framework conditions. On the other hand, some notified bodies might consider the cost-benefit ratio for the certification of substance-based medical devices unfavourable and therefore refuse certification. Inability of manufacturers to find a notified body who certifies their products will inevitably endanger marketability of these products.

From 2020 substance-based medical devices will also have to meet more stringent essential requirements: They will have to prove their safety according to rules which are applicable to medicinal products. These rules are tailored to medicines which are systemically available in the human body. For this reason, medical devices are not able to fulfil many of the requirements for market approval of medicinal products because they do not work by a pharmacological, immunological or metabolic mode of action. As a result, many of these products may no longer be available for patients, as they can no longer be marketed.

Most substance-based medical devices are ‘low risk’

Substance-based medical devices are health products which have been used safely for years which are considered to be so-called ‘low risk’ products. They are of great importance for patients and generate annual revenues in high triple-digit millions Euro in Germany.

The new requirements for market access of substance-based medical devices should above all be implemented in a feasible manner. It should not be neglected that the majority of substance-based medical devices have been marketed for decades without any incidents. Strict implementation of the high hurdles for market access would be disproportionate.
The GCP (Good Clinical Practice) Regulation 536/2014 of the EU establishes a new authorisation procedure for clinical trials. The ‘European Medicines Agency’ (EMA) which shall support the new procedure with an online portal and a database, lags behind schedule.

Clinical trials can have different designs. They can, for example, examine medicines which are not yet approved for marketing or compare them with others which are already approved. Research in humans must not be started without the consent of regulatory authorities and ethics committees of all countries which are involved in the concerned trial. Up to now, the sponsor of a clinical trial had to submit a separate application for authorisation in each member state, with the different formats, timelines and languages. Each protocol change has to be agreed by all countries involved.

Central instead of national authorisation

The EU GCP Regulation establishes a new authorisation procedure. It replaces the separate national authorisations by the concept of mutual recognition. This means that in the future one application per trial within the EU will be sufficient. The pharmaceutical manufacturer submits one application to all EU Member States in which clinical trial sites are located (clinics or medical practices) via the central online portal of the EMA. The assessment of the application is then performed by the competent authorities and ethics committees of the respective countries. Ultimately the manufacturer receives one final authorisation. Pursuant to the regulation, the implementation of the new rules is linked to the operability of the portal and the database at the EMA. According to information given by the EMA this will be assured on October 2018 at the latest.

Delay allows more time for implementation

The concept of mutual recognition creates common standards for authorisation procedures of clinical trials in the EU. The project, however, lags behind schedule. Despite this facilitation of the procedure, commercial sponsors and competent authorities deem the delay not purely negative: it gives all stakeholders more time to get prepared for the new workflows. And to get prepared for the fact that for a period of three years the newly organized processes must be run in parallel to the previous ones, requiring enormous effort from all stakeholders. The EMA also envisages disclosing significant contents of the database on clinical trials to the public. The pharmaceutical associations criticize this intention because it deprives the manufacturers of their data sovereignty. This may cause major problems for larger companies whose data are normally indirectly protected by patents or protection certificates. Smaller companies, however, who tend to engage in the improvement of known active substances with expired patent protection, for example in the optimisation of the route of administration or a new presentation, see their work surrendered to competitors without any protection.

BAH is directly involved in the development of the portal and the database via its European umbrella organization, the ‘Association of the European Self-Medication Industry’ (AESGP). Together with the EMA, the national competent authorities and other industry associations, BAH engages actively in the design of the contents and concepts for implementation of the legal requirements.
Health claims

ASSESSMENT OF HEALTH CLAIMS FOR ‘BOTANICALS’ NECESSARY

Within the EU, manufacturers of food including food supplements must prove so-called ‘health claims’ for the respective products and apply for authorization of these claims at the European Commission. This assessment has been suspended for plants and their preparations used in foods. In contrast to this, herbal medicinal products – often mixed up with food supplements by consumers – must undergo an assessment and marketing authorisation procedure.

‘Strengthens your natural body’s defenses’, ‘Promotes energetic metabolism’, ‘Contributes to the normal function of your immune system’ – health claims like these can often be found on food packaging notably on food supplements. Particularly in the case of products containing plants, consumers can barely distinguish between botanical food supplements and tested and approved herbal medicinal products.

An EU Regulation stipulates the formal requirements for health claims on food. Pursuant to this regulation, health claims are only allowed if they have been established by generally accepted scientific data, if they are authorised in accordance with this regulation and if they are included in a positive list of authorised claims.

Harm for consumers and manufacturers

In 2010, the European Commission suspended the assessment of health claims for botanical ingredients for an indefinite period of time. It can be assumed that many of these health claims would not stand up to scrutiny, as the health-preserving effect cannot often reliably be proven. The suspension of the obligation of the manufacturers of the respective products to provide evidence for the claims harms consumers and manufacturers of food supplements and medicinal products. Consumers are potentially misled if they trust in claims that are not scientifically based. Manufacturers of food supplements containing plants must fear damage to their image, as long as the EU does not confirm evidence for their health claims. The manufacturers of herbal medicinal products are confronted with competitive disadvantages because in contrast to food supplements their products must undergo an official assessment and marketing authorization procedure which hampers market access.

No alternative

In 2012 the EU posed an alternative for discussion: Health Claims which have been used for a long period of time should be legitimized due to this ‘tradition’ and by borrowing the scientific evidence for traditional herbal medicinal products. This alternative is questionable because it would undermine the original intention of the health claims regulation, i.e. to generate evidence for health claims on food and to improve consumer protection. The result would be products which are similar to medicinal products but do not fulfil the requirements for marketing authorisation of medicinal products. For the consumers the differences between an assessed and authorised medicinal product and an unexamined botanical food supplement would become even more obscure.

Consequent implementation of the EU regulation is better

Consequent implementation of the health claims regulation would not only create benefits for the consumers by providing them generally with deeper confidence in health claims on food. Uniform EU-wide regulation of health claims for food and food supplements as currently stipulated by the European health claims regulation would also be positive for the free movement of goods.
SUSTAINABLE ACCESS TO MEDICINES IN EUROPE

HARMONISED ASSESSMENT FACILITATES MARKET APPROVAL

Applications for marketing authorisation or registration of herbal and homoeopathic medicinal products should be as unbureaucratic and easy to handle as possible for manufacturers. At the level of the EU, harmonised criteria for the assessment of safety and efficacy of the products are an integral part of this concept.

In 2016, non-prescription herbal and homoeopathic medicinal products – from self-medication and upon medical prescription – generated a turnover of approximately EUR 2 billion in German pharmacies. This corresponds to about 31 percent of the total pharmacy turnover from non-prescription medicinal products.

In contrast to chemically defined medicinal products, herbal medicinal products contain pharmaceutically processed preparations of herbal drugs. Homoeopathic medicinal products can be of herbal, animal, mineral, chemical or human origin.

In Germany, herbal medicinal products must pass several control instances within the Federal Institute for Drugs and Medical Devices (BfArM) before they can be dispensed to patients in pharmacies. The manufacturers must submit documentation of the production and high quality standards of the medicinal product. Safety and efficacy must likewise be proven by bibliographic data or investigations by the manufacturer.

The herbal sector is mostly regulated at the EU level

The Herbal Medicinal Products Committee (HMPC) is situated at the ‘European Medicines Agency’ (EMA). Since 2004 it has produced almost 150 assessments of single herbal drugs and preparations thereof in the form of monographs. The multitude of monographs covers a broad spectrum of therapeutic areas. In addition, the HMPC assumes responsibility for a multitude of guidelines for the assessment of the quality, safety and efficacy of herbal medicinal products. Such harmonised assessment criteria contribute to the facilitation of applications for marketing authorisations of herbal medicinal products with an acknowledged medicinal use. The same applies to the use of herbal medicinal products in children. Within safety evaluations of the HMPC, especially for those herbal medicinal products which have already been marketed for a long time, it should be thoroughly balanced to what extent toxicological worst-case calculations with reference to single constituents are appropriate, as the preparations are complex mixtures of many substances.

Assessment of product-related claims needed

Herbals, including traditional herbal medicinal products, which have always been obliged to undergo an official marketing authorisation or registration procedure, must be preserved as a part of the treasure of medicinal products. This deserves special attention as European authorities still fail to implement the European health claims regulation for food supplements with herbal ingredients. Furthermore, herbal medicinal products and food supplements often bear similar product claims. The basic requirements of the European regulation concerning the scientific proof of health claims for food supplements are also appropriate for herbal ingredients. Only this warrants that the consumer obtains products with scientifically evaluated health claims.

Pharmacovigilance and variations: Taking particularities into account

Reasonable implementation of the European legal framework must take the particularities of herbal and homoeopathic medicinal products into account. This applies for example to the pharmacovigilance rules. Reports on adverse events for herbal and homoeopathic medicinal products are relatively rare. Likewise, it should be possible to perform variations including their approval procedures without great bureaucratic expenditure. In the case of complex natural substances, variations relating to analytical procedures are quite frequent and mostly without
any safety relevance. Streamlining of the dossier for herbal and homoeopathic medicinal products might be a further measure for de-bureaucratization.

**Alleviations for homoeopathic medicinal products with indications**

So far, only very few Member States offer the opportunity to obtain a marketing authorisation with specified indications for a homoeopathic medicinal product. Increased use of this legal option of the EU would be desirable. It would facilitate mutual recognition of marketing authorisations for herbal and homoeopathic medicinal products with therapeutic indications. In this context, bibliographic data should also find more acceptance in marketing authorisation procedures for homoeopathic medicines.

*Coneflower (Echinacea) is a frequently used medicinal plant.*

| Harmonized assessment criteria contribute to facilitated market access for herbal and homoeopathic medicinal products. |
Paediatric medicinal products

IMPROVE INCENTIVES FOR PAEDIATRIC STUDIES

Therapies with medicinal products often expose children and adolescents up to 17 years of age (hereinafter referred to as ‘children’) to special risks. Medicinal products have not always been tested in this population, and marketing authorisations for them are likewise lacking. The development of paediatric medicinal products on the basis of existing products which are long time approved for adults is not obligatory. A better incentive policy for voluntary research could help.

Only 150 out of 1,200 clinical studies per year in Germany include children as study subjects. The EU ‘Regulation on paediatric medicinal products’ of 2007 aimed to create more medicinal products which are safe, age-adapted and have been tested in children. It made paediatric studies obligatory for the development of new medicines and has by this achieved an improvement of the situation in the area of new medicines: According to information provided by the ‘European Medicines Agency’ (EMA), and the ‘Paediatric Committee’ (PDCO) which is in charge of the assessment of paediatric studies, the number of marketing authorisations for children solely in the centralised procedure has more than doubled: from 31 in the period from 2004 to 2006 to 68 in the period from 2012 to 2014.

Few research incentives for PUMAs

The situation for medicinal products which are already approved for adults for a longer time is different. For these, paediatric research by the marketing authorization holder is voluntary. An authorization for the paediatric use of a medicinal product which is already approved for adults is called ‘PUMA’ (Paediatric Use Marketing Authorisation). Such an authorization can be granted for all paediatric indications, for all or specified age groups or for the development of pharmaceutical forms which are suitable for children. The compensation for the holder of a PUMA is a ten year data protection. This market exclusivity for the product should at least compensate for the financial research expenditure. However, it seems to exist only in name because it is undermined by national health systems, and not only in Germany. Substitution of medicinal products with the same active substance according to the aut-idem rule basically obstructs market-exclusivity. In addition, in Germany PUMAs must undergo the sophisticated procedure of the early benefit assessment conducted by the Federal Joint Committee (G-BA).

IKAM-initiative argues for improvements in the existing market

As a member of the ‘Initiative Medicines for Children e.V.’ (IKAM), the BAH is committed to medicinal products which are safe and have been tested in children. Consistent implementation of the PUMA concept pursuant to the EU regulation could improve the situation in terms of the existing market. The benefit of a PUMA should in the future – similar to orphan medicinal products which are intended for the treatment of rare diseases – be considered as established, as the medicinal product has already cleared high regulatory hurdles. The G-BA should merely assess the extent of the benefit. Furthermore, intelligent incentives are needed in order to bring the development and marketing of medicinal products which have specifically been developed for children also to economic success.