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# Contents

*Prof. Dr. Karl Broich*
*President of the BfArM*

*Prof. Dr. Julia Stingl*
*Vice President of the BfArM*

Dear reader,

On the basis of its strategic orientation the BfArM puts important developments on the right track for the future. A pivotal point is the development of our fields of action: In what direction will regulatory requirements go? How will technological and scientific innovations change our work? What demands will be made on authorisation, pharmacovigilance and research?

In the change processes of the recent years the BfArM has noticeably contributed to the further development of the frame conditions of our work and our options to act. Here are some of the challenges we have faced: growing demands on advice to pharmaceutical companies, ever more complex study designs in clinical trials, new ways of data analysis. We keep in constant touch with all our stakeholders in order to be able to act adequately on behalf of the patients. We have also discussed our strategic orientation for the next ten years together with them. A crucial issue is early market access for new and innovative medicines. It is our task to find ways that satisfy both our regulatory requirements and the interests of the patients alike.

The BfArM is one of the leading medicines agencies in Europe. We are part of an international network which we actively help to shape. We are connected with many research institutions and universities to the benefit of our scientific

expertise. Our own research department contributes a great deal to our reputation in Europe.

The BfArM is well-positioned for the future developments. We have competent and committed staffs in the regulatory, scientific and administrative units. So we look optimistically at the changed conditions which have brought us new tasks and new orientations. Yet, in the heart of all our activities is and will be the supply of safe and efficient medicinal products and medical devices to the population.

Prof. Dr. Karl Broich
President of the BfArM

Prof. Dr. Julia Stingl
Vice President of the BfArM

# Faster Supply of Innovative Medicinal Products

Prof. Dr. Karl Broich on the role of the BfArM in supplying patients with innovative medicinal products, on the handling of ever more complex study designs and on the growing importance of data analysis.

*Prof. Dr. Karl Broich*
*President of the BfArM*

**Pharmacovigilance is of increasing importance. Potential risks should be detected faster and faster while more and more data sets need to be evaluated for it.**
**What does this mean for the tasks of the BfArM?**

We principally welcome this development, since more data mean better possibilities for risk assessment. At the same time growing data sets pose new challenges since they must be administered, processed and analysed. The national ADR reports are compiled in a special data base of the BfArM, where monitoring is done in the form of structured analysis to discover relevant signals and discuss them on a European level. The data are also transmitted to the European Medicines Agency (EMA), which has its own data base, "EudraVigilance", for the evaluation of the reports. They, in turn, send us structured data as well, which we then analyse.

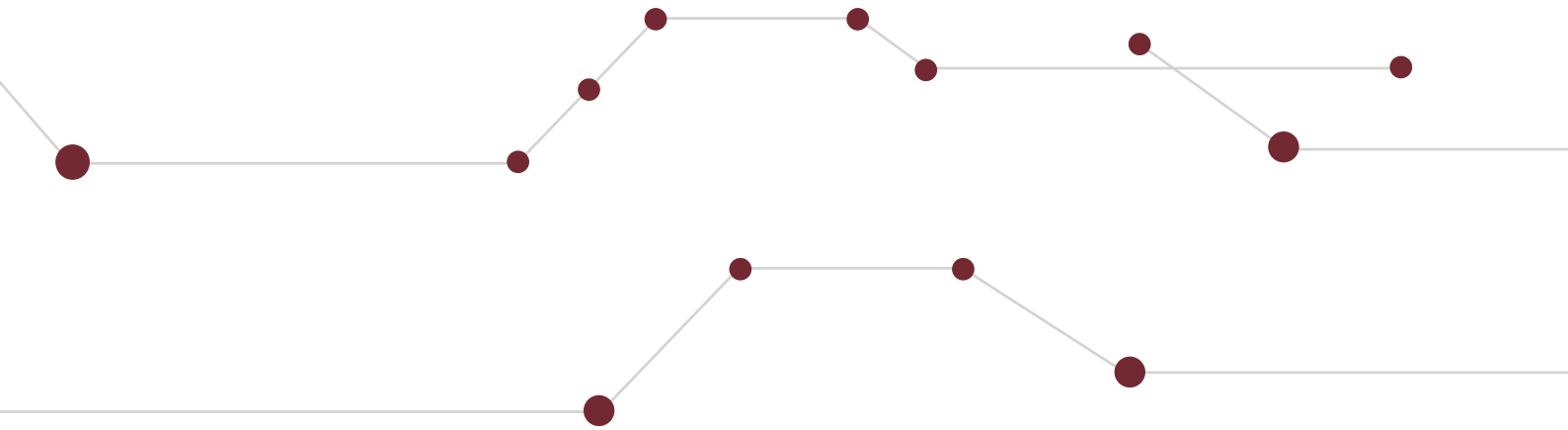
A few months ago the "Medical Literature Monitoring" project was launched, with the help of which medical publications can be systematically screened for reports on side effects of certain substances.

All this shows that the search for early risk signals is getting more and more important. The analysis of all these data requires a high level of scientific and regulatory expertise. In the end the system of pharmacovigilance is improving thanks to these developments, but at the same it is getting increasingly complex.

### How does the BfArM respond to this development?

Not only do we accept the development, nationally and on the EU level, but we play an active part in it. After all, the work of our institute is judged by our attitude to this development. For example, the discussions about anticoagulants, such as Pradaxa or Xarelto, have demonstrated where it will end up if the public is not given a well-balanced description of benefits versus potential risks so that worried patients turn to us for information. In future we will intervene in discussions sooner and more actively. The people do rightly ask for well-founded and independent information about drug-related risks. Well, I see it this way, nobody can really get around BfArM's assessments here. One of our key tasks is assessing product risks on the basis of data and facts and relating them to the product benefits. Last but not least the BfArM does its own research exactly into these issues, which is essential to our daily regu-

The BfArM, in cooperation with partners from research and industry, is currently developing new methods for the systematic use and evaluation of large data sets, as are available in scientific publications on medical technology or in administrative and public data bases, to support the monitoring of medical devices on the market. See more on page 38.



latory business. Our staff is well connected in the European context and does excellent work in the corresponding committees of the EMA.

**What about risk identification in medical devices? Is the evaluation of data of similar importance here?**

The development is indeed similar. Risk assessment for medical devices is likewise a core competence of the BfArM. Large amounts of relevant information is found in administrative or public data bases and, of course, in scientific publications on medical technology. For the best possible evaluation of these sources we are developing a risk identification software, in cooperation with partners from research and industry. It is designed to help us observe medical devices on the market and identify potential risks at an early stage. Such a software would also give the manufacturers of medical devices a better chance to detect and minimise risks. This is in the direct interest of the BfArM and the other national and European authorities. Dealing with such innovative tools of analysis is of growing importance. We deliberately want to grab the chance to be Europe's trailblazer when it comes to the fast acquisition of new information and the evaluation of new risks of medical devices.

**In other areas more data would be welcome. Supply shortages of medicinal products are currently reported by manufacturers on a voluntary basis. Is this enough?**

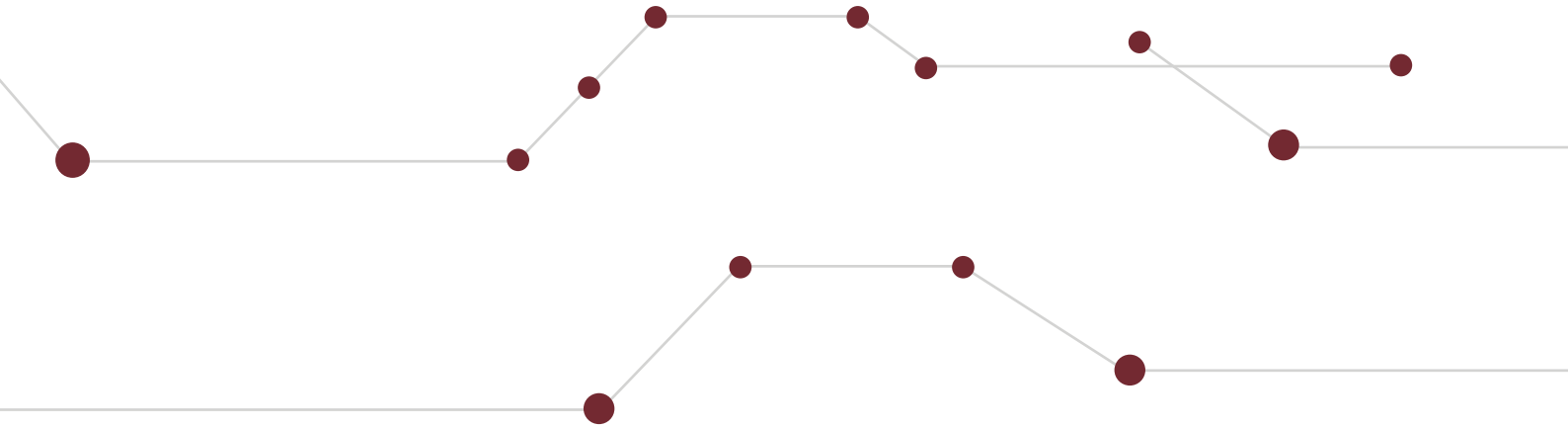
Considering that we need adequate supply of medicines this is certainly not a satisfactory solution in the long run. If, for instance, a vital anticancer medicine cannot be supplied over a couple of weeks, this is bound to have an impact on therapy. Therefore, I have been arguing for some time now for a company commitment or a statutory obligation to report shortages of important medicinal products so that appropriate measures can be taken. And, hopefully, companies would also arrange for precautions then. Also longer stockpiling is being considered for very important medicinal products threatened with supply shortage.

**How is the BfArM handling the situation?**

Not every supply shortage causes inadequate patient care since there are either alternative treatments available or other manufacturers to switch to. Because of the complexity of causes we keep contact with all stakeholders for better coping with the situation. We have talks with the drug commissions of the physicians and pharmacists including the hospital pharmacists, as well as with the associations of the pharmaceutical industry. On the basis of the lists of indispensable medicinal products of the WHO and the medical associations, we have compiled a risk-based list of medicinal products for which there are not enough therapeutic alternatives to switch to and for which there are only one or two manufacturers. Shortage of these medicinal products would result in inadequate patient care. Currently this shortage list includes about 100 products for which adequate reserves ought to be built up.

**New challenges are becoming apparent in the fields of advice giving and clinical trials with study designs of growing complexity. How is the BfArM preparing for these tasks? The pharmaceutical companies demand greater convergence of requirements in product authorisation on the one hand and in benefit assessment on the other. What is BfArM's position here?**

With a view to the Act on the Reform of the Market for Medicinal Products (AMNOG), I should like to point out that the tasks of the BfArM differ from those of the Federal Joint Committee (G-BA). Our task is the assessment of the benefit-risk ratio in a medicinal product, while the G-BA is concerned with the question whether the benefit of a novel medicinal product is superior to the benefit of a known and established comparative therapy. For the latter the pharmaceutical company submits a dossier demonstrating the additional benefit on the basis of the authorisation documents and all the studies performed. It is a long tradition that the BfArM gives advice to the pharmaceutical companies as regards the specific requirements for authorisation studies; the dossiers submitted to the G-BA, however, usually need to present additional data relating to the so-called appropriate comparative therapy (ZVT) or to more patient-relevant endpoints. Yet, despite the differing tasks, there



*"All stakeholders are interested in providing good health care for the population."*
***Prof. Dr. Karl Broich, President of the BfArM***

are several points of common interests. We cooperate closely with the G-BA, also in the light of converging requirements, and have begun to offer joint consultations. It is in the interest of all stakeholders to provide appropriate and high-quality health care for the population. Professional dialogue will be important for the success of our shared task.

**There are growing demands for giving patients earlier access to innovative medicinal products.**
**What is the role of the BfArM with regard to "Adaptive Pathway" and "PRIME"?**

***PRIME (Priority Medicines)***
*PRIME (Priority Medicines) is a scheme launched by the European Medicines Agency (EMA) to enhance the support for the development of medicinal products that target an unmet medical need. The Agency offers early and proactive support, e. g. by optimising development plans, to enable accelerated authorisation so that these medicines can reach patients earlier.*

Regrettably, there are still many diseases for which we do not have adequate therapies, for instance for a number of cancer disease and for very rare diseases. This situation is usually referred to as 'unmet medical need'. It is understandable when patients in cases of serious life-threatening diseases or in cases where they would suffer severe impairment without treatment, wish to get the fastest possible access to new medicines. That is why the European Commission in the STAMP working group and the European authorising agencies, in their strategy document, have put down their commitment to take care that patients have faster access to new and innovative medicinal products.

**How can this be accomplished?**

The pharmaceutical regulations have already been provided, they only need to be used more efficiently and more flexibly. The PRIME initiative of the European Medicines Agency has the strictest plan for its implementation, similar to the "Breakthrough Therapy Designation" programme of the FDA. Today innovations often spring up from academic centres or small and medium-size start-up-companies. They have very good ideas there, but they are inexperienced in the regulatory decision-making processes so that they tend to make the wrong decisions. This is the reason why many development programmes fail. It is the declared aim of the PRIME initiative to avoid such mis-

takes by bringing applicants very early together with rapporteur teams and regulatory experts – from early scientific advice through to the decision on authorisation. Then applicants and companies know from the very beginning what kind of data we require and what we want them to submit. In the end it is up to us to grant or refuse authorisation, in either case we must be able to justify our decision. Despite the responsibility that rests on our shoulders we remain calm and placid in this process.

**What do you say about critical comments on this initiative? Will it really undermine the standards?**

These models are designed to find a way that satisfies both our requirements as an authorising agency and the interests of the patients concerned. One idea is that instead of performing tests directly in a big patient population, studies could be started with those patients who are most likely to profit from the new therapy. Critics call this a limited data base and reduction in standards, which is not true at all. Evidence of the efficacy of a new therapy is even higher in a more strictly defined patient group. And if a medicinal product with an initially restricted authorisation is wished to be used more widely, applicants are required to generate more data on efficacy and safety. We are just learning to what extent it is necessary to have additional evidence from the classical, randomised, controlled studies on the one hand and to what extent the so-called "real world" or health care data will do on the other hand. In what way the product will develop and which indications may be added, will crop up in the course of time. Indispensable is the early involvement of the HTA bodies competent for the assessment of health-related technologies: in the wake of the further development of a product and a possible extension or specification of indications it will be necessary to adapt and update the additional benefit assessments. As a result, we will have growing numbers of conditional authorisation with the imposed conditions to be fulfilled in defined time slots. Accordingly, we are likely to see more temporary additional benefit assessments then. The BfArM wants to use the Adaptive Pathway and PRIME pilot phases for their further development and make an active contribution to it.

***STAMP***

*The expert group STAMP (Commission Expert Group on Safe and Timely Access to Medicines for Patients) has been established to advise the agencies of the European Commission on implementation of EU pharmaceutical legislation, programmes and policies. The group exchange their views on opportunities and initiatives in the EU Member States to use the existing regulations more efficiently to enable early access to new medicinal products.*

***Breakthrough Therapy Designation***

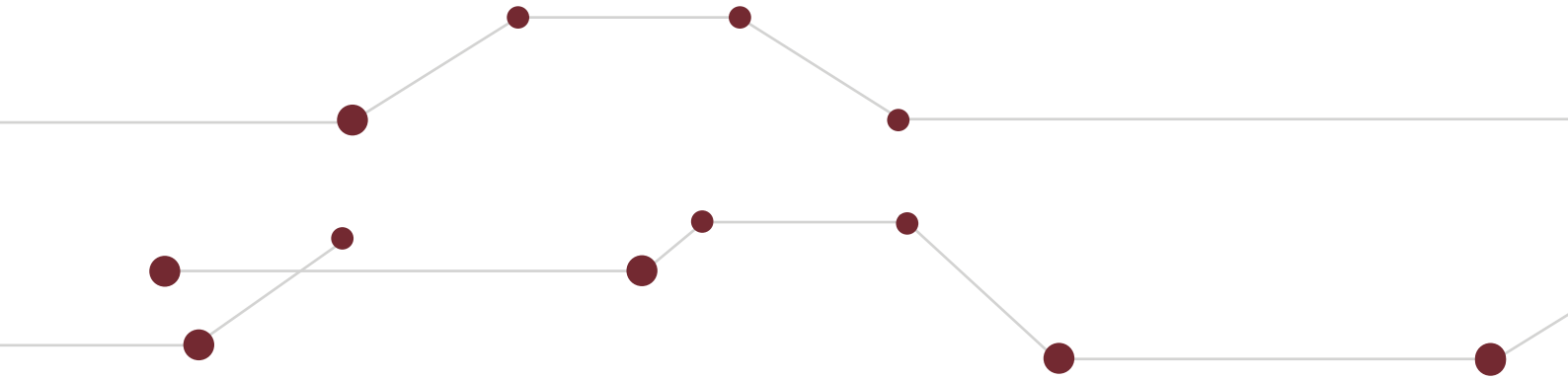
*Under the FDA (U.S. Food and Drug Administration) programme accelerated market authorisation is provided for medicinal products that are eligible for breakthrough therapy designation, i. e. are promising medicines for the treatment of serious diseases.*

**Have these developments played a role in the 'Pharmadialog' of the Federal Government?**

Yes, they have. And it is reflected in the report of the Federal Government. It was very good that the BfArM and the Paul-Ehrlich-Institut (PEI) were intensively involved. We presented our positions on a number of key aspects, thus giving practical political advice. In certain parts of the dialogue I was more strongly and actively involved; for instance in the question of avoiding resistances to antibiotics, or where possible incentives for the development of novel antibiotics were discussed; or about improvements in the handling of supply shortages or the structured cooperation with the G-BA.

**Is the BfArM well prepared for the multifarious developments?**

Yes, we definitely are! We have competent and committed colleagues in the regulatory, scientific and administrative areas. We do provide for the changing conditions by critically reviewing the new tasks and by a general reorientation. It is not always easy to integrate new tasks and priorities, particularly since the concentration of work has strongly risen at our institute as well. Yet, the commitment of our staff and new electronic technologies help us to cope. We also bank on our close connections with national and European partner agencies. We extend our scientific expertise in cooperation with research institutions and universities, e. g. with the faculties of the University of Bonn, the German Center for Neurodegenerative Diseases (DZNE) and the German Centre for Infection Research (DZIF), with organisations of medical device registers, and many others. This is a chance for work-sharing, but also for multiplying our knowledge. Communication with professional circles and applicants from the industry takes place on an equal footing.



**How do those concerned judge this commitment?**

We are in constant touch with patient representatives to learn about their expectations and judgments. It is essential that we give due consideration to the patient perspective, for instance in debates on trial endpoints or potential risks: What are appropriate patient-relevant endpoints? Which side effects are still acceptable for a certain spectrum of efficacy? At the end of the day, patients shall get the medicinal products and medical devices they need, and they shall get them promptly and without being exposed to unjustifiable risks. Our decisions are always based on the latest state of knowledge. In order to fulfill our tasks successfully we have discussed our Strategy Plan 2025 with all our partners, and now we are going to implement this plan.

# Closing the Gap in Supply of Medicines for Children

BfArM and Federal Ministry of Health want to strengthen paediatric authorisation of patent-free medicinal products.

The BfArM has long been committed to improving the situation of medicinal products for children and adolescents. Many authorised medicinal products are administered to children although no systematic clinical trials on dosage or pharmaceutical form are available. Instead, doses are often merely adjusted to the body weight although the metabolism of adults and children may differ considerably depending on the child's development phase. Doses determined for adults may be too high or too low or doses are given too rarely or too often. As a result, medicinal products may have a restricted or even no effect. The worst case would be the occurrence of severe side effects. Also the appropriate pharmaceutical form is a problem in this context. Medicinal products available for adults in the form of tablets, often need to be crushed for children and mixed with liquids or food. In such cases it is often not possible to ensure precise drug dosing. Besides it is not well enough tested to what extent the action of a medicine is affected by added foods.

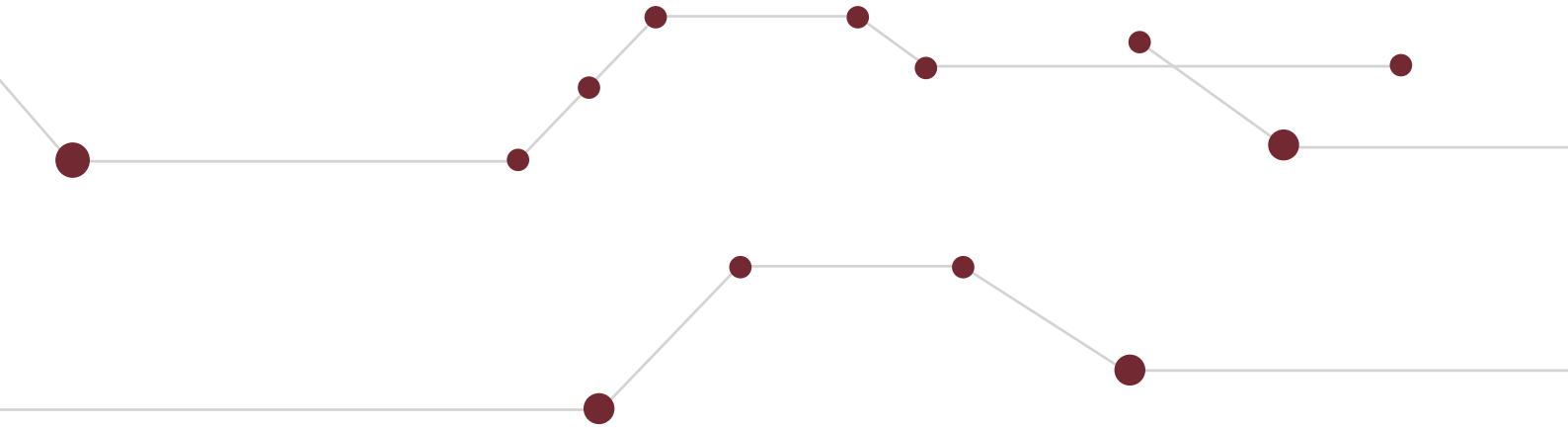
"We want to make sure that a growing number of safe medicinal products for children is placed on the market", states Prof. Dr. Karl Broich, BfArM President. In the first place the BfArM thinks of already available and patent-free

Only two successful PUMA applications have been made in the EU since 2007. Therefore, the BfArM has made it its business to identify and remove obstacles and stimulate this way of authorising medicinal products for paediatric use.

medicinal products. Yet, the authorisation procedures provided for the purpose of safe use of such medicines in children are scarcely made use of by pharmaceutical companies. “The further development of such medicinal products could quickly close the gap in the supply of medicines for this age group“, says Broich.
To encourage this development the BfArM, in cooperation with the Federal Ministry of Health, initiated a dialogue with all stakeholders. A BfArM symposium specifically arranged for the topic of paediatric medicines was also a campaign for a stronger use of the “Paediatric-use marketing authorisation – PUMA“, which was implemented in 2007 for the purpose of supporting medicines for children. This procedure grants PUMA holders a ten year period of data and market protection for the proposed paediatric indications. This means that other manufacturers of the generic medicinal products in question are not allowed to cross-refer to such authorisation for a period of ten years, neither can the latter receive authorisation for these paediatric indications and pharmaceutical forms without having performed their own clinical trials. However, in order to benefit from this far-reaching data and market protection pharmaceutical companies are obliged to submit for approval a paediatric investigation plan to the Paediatric Committee (PDCO) of the European Medicines Agency, and to develop the medicinal product according to the lines defined in the Paediatric Committee decision.

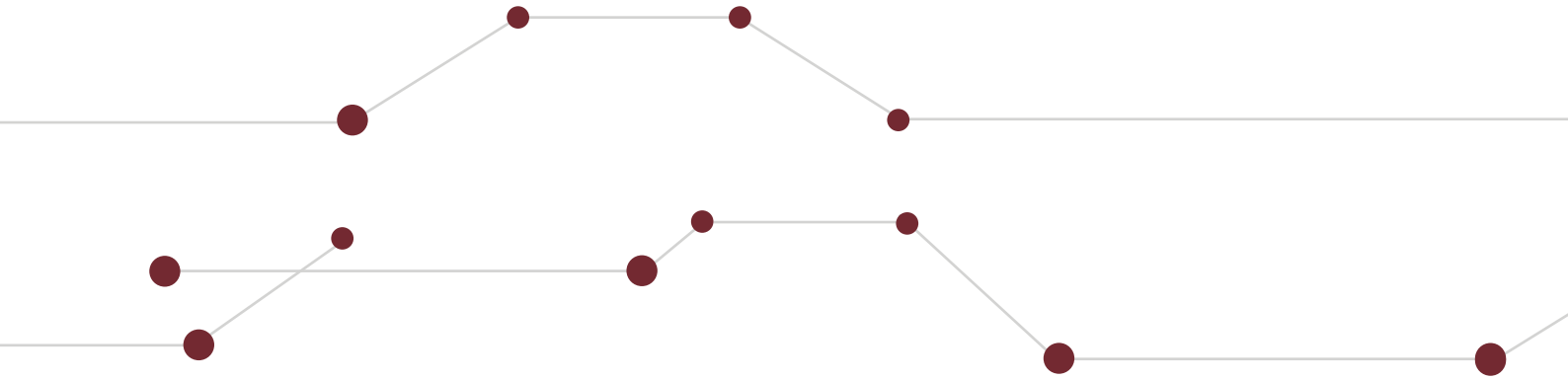
Only two successful PUMA applications have been made in the EU since 2007. Therefore, the BfArM has made it its business to identify and remove obstacles and stimulate this way of authorising medicinal products for paediatric use. “The pharmaceutical companies should be cooperative and ready to continue research on their products“, states the BfArM President.

Besides we need sponsors, possibly from the pharmaceutical industry or university hospitals, of clinical trials for the transfer of medicinal products for adults to those for children. And we need the cooperation of medical doctors to conduct systematic investigations as clinical trial investigators. Last but not least educational activities must be intensified to increase parents’ readiness to allow their diseased children to participate in clinical trials. Parents want to have as much information as possible on the use of medicinal prod-



ucts in children, but are very reluctant to have their children participate in clinical trials .“More information and confidence-building measures must be provided“, says Broich.

“We also give advice to manufacturers and take care that their specific applications are processed swiftly.“ The BfArM will keep contact with all stakeholders and work together on solutions, first of all with the expert groups with whom we agree on the prioritisation of medicinal products. The quickest possible way towards a special paediatric authorisation on the basis of appropriate trials should be found for the selected products.



## Background: PUMA

Paediatric use marketing authorisation is a new form of authorisation of medicinal products. This special additional authorisation can be granted to any medicinal product that is already authorised for adults and for which further authorisation is sought solely for use in the paediatric population. Such authorisation can be granted for all paediatric indications in all or in selected age groups and for the development of dosage forms appropriate for children. Development for use in children must comply with the paediatric investigation plan approved by the Paediatric Committee.

# Dialogue between BfArM and G-BA Getting More Intensive

The exchange serves cost effectiveness, innovations and high-quality patient care.

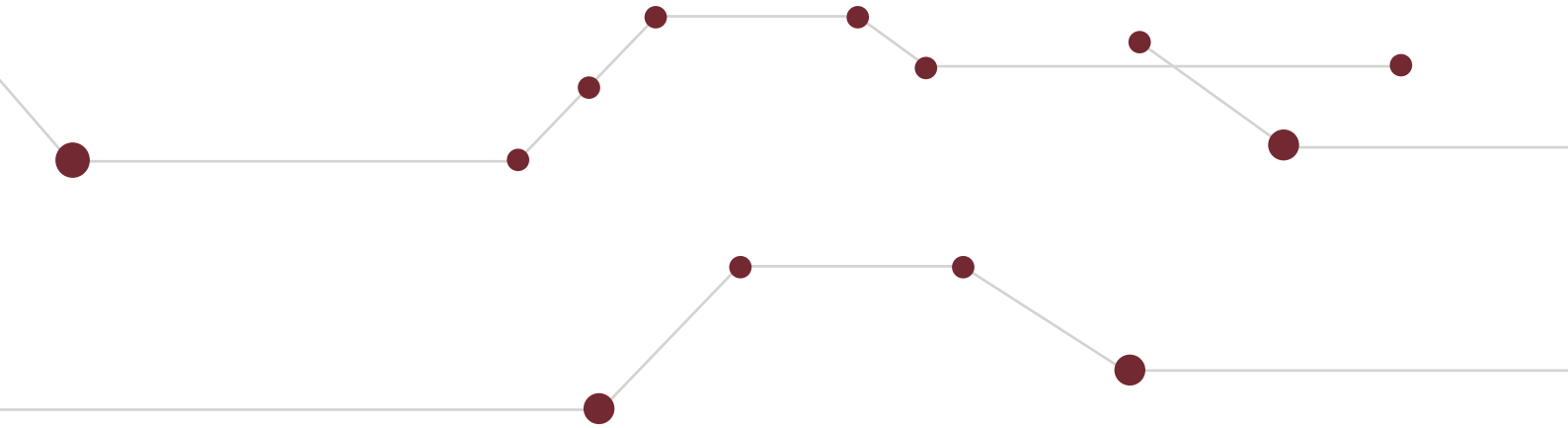
The Act on the Reform of the Market for Medicinal Products of 2011 (AMNOG) provides that products are subject to early assessment of an additional benefit after market launch. The pharmaceutical company submits a dossier in which the additional benefit is demonstrated mainly on the basis of the authorisation documents, to the Federal Joint Committee (G-BA). If it is recognized that an additional benefit exists over an appropriate comparative therapy (ZVT) as previously specified by the G-BA, the National Association of Statutory Health Insurance Funds (GKV-Spitzenverband) negotiates with the pharmaceutical company a surcharge added to the price of the ZVT. The BfArM offers consultations to pharmaceutical companies for the preparation of a dossier and is going to intensify cooperation with the G-BA, which appears reasonable in view of the foreseeable convergence of requirements.

Pharmaceutical companies are faced with the challenging task to design clinical trials in a way that they meet not only the requirements of the regulatory authorities for different markets but also the G-BA requirements for early additional benefit assessment. Since other countries have also implemented complex health technology assessment (HTA) procedures, the usually

The Federal Joint Committee (G-BA) is the highest decision-making body of the joint self-government of physicians, dentists, psychotherapists, hospitals, and health insurance funds in Germany. In legally binding regulations the G-BA specifies the catalogue of services under the Statutory Health Insurance, i. e. it specifies which services are reimbursed. The G-BA decides on measures of quality assurance in the medical care in clinics and doctors' practices.

multinationally conducted studies must come up to their requirements as well. That is why scientific advice afforded by the involved institutions is of growing importance. Already in the process of authorisation the BfArM assessors obtain essential knowledge about the benefit of a new medicine. The pharmaceutical benefit is usually investigated in the framework of controlled clinical trials. Therein the efficacy and side effect profile of the investigated product are compared to an established therapy (comparator) or placebo. In most cases the comparator is applied in accordance with the data provided in the authorisation texts in Germany. But the regulatory authorities in the EU accept an active comparator as long as it is listed in the specified dosage in expert guidelines of at least one Member State. This allows pharmaceutical companies to conduct large multinational clinical trials even if authorisation texts and treatment standards deviate in the involved countries.

The outcome of an authorisation procedure plays an important role in the subsequent additional benefit assessment by the G-BA, since the assessment is based on the clearly defined indication in the authorisation dossier. Additional benefit means that the benefit is quantitatively or qualitatively higher than the benefit of the ZVT. Besides, the ZVT must be authorised in Germany in the proposed indication and dosage. This means that the ZVT is more closely defined than the comparative therapy referred to for authorisation purposes. Here the BfArM can be helpful at an early stage since its assessors know all the relevant endpoints and comparative therapies and can provide valuable information in consultations. In the work with the G-BA it has turned out that there are uncertainties about the ZVT and endpoints of clinical trials. We made this issue a topic at the BfArM dialogue "Gemeinsam Gesundheit gestalten - Strategie BfArM 2025" (joint programme for health - strategy BfArM 2025). Some pharmaceutical companies noted that the demands made by the regulatory authorities would differ from those made by the HTA bodies. While the BfArM would assess the benefit-risk-ratio, the G-BA would focus on the question whether the benefit of the proposed product is higher than the benefit of a comparative therapy. The reasons for the discrepancy are as follows: authorisation procedures and early benefit assessment of new medicines belong to different legal domains, viz. to pharmaceutical legislation and to social legislation, respectively; they pursue different purposes and hence refer to different assessment programmes.



Irrespective of the different tasks, it is legitimate to ask for convergence of the requirements. Many of the parameters important for the early benefit assessment could be identified without greater efforts in connection with the studies submitted in the authorisation procedure. Many of the endpoints selected for the authorisation are not accepted in the additional benefit assessment, take, for example, the measurement of progression-free survival in cancer disease. The discrepancies between the G-BA and the involved pharmaceutical companies include such items as the specification of the ZVT, the definition of relevant subgroups, the acceptance of patient relevant endpoints and the classification and grading of side effects. A change is only possible if pharmaceutical companies do seek advice prior to the beginning of Phase III studies and if the HTA bodies and the regulatory authorities can harmonise their requirements. Because of the need for harmonisation, BfArM President Prof. Dr. Karl Broich and G-BA Chairman Prof. Josef Hecken decided to establish the early advice as a routine procedure at the G-BA and the BfArM. Also the exchange of data shall be improved and the dialogue between the two houses intensified. Assessors will have the opportunity to work in the other house for a certain time to get to know the on-site structures and gain deeper insight into their work processes, so that in the end we will have a network of contact persons. Such exchange between the two houses will serve cost effectiveness, innovations and high-quality patient care.

# Perspective of those Concerned is of Interest

Feedback from patient representatives is valuable information for the regulatory agencies. Our cooperation with patient representatives shall be extended in the future.

Feedback from patients, for instance about their experience with a medicinal product or how the quality of life is influenced by certain therapies, provides valuable information to regulatory agencies. Also with a view to new ways of drug authorisation it is important to know the perspective of those concerned. Therefore the BfArM, together with the Paul-Ehrlich-Institut (PEI), has intensified the dialogue with self-help organisations. As for the European level, possibilities of cooperation have been explored and the framework for the participation of patient representatives in centralised procedures discussed at various related meetings. A respective pilot project shall be launched soon.

“The patients’ expectations are of increasing relevance to regulatory decisions“, says BfArM President Prof. Dr. Karl Broich. “They play a key role in the implementation and optimisation of treatment strategies and they can even stimulate new procedures.“

The experience of those concerned is crucial to the agencies when considering the development of new types of therapy for certain diseases. New forms of drug authorisation, like adaptive licensing, bring new challenges to both

As early as 2004 involvement of patient organisations in the shaping of the national health system became statutory. Accordingly it is stated in the Code of Social Law (SGB): “The organisations decisively committed to the safeguarding of patients’ interests and the self-help groups of chronically ill and handicapped persons, shall be involved in all issues relating to patient care (...).“

sides. For instance, innovative drugs should be authorised quickly to help affected persons. Yet, the data available for the product in question are necessarily limited at the time of authorisation. In such cases the experience of patients with the product is a crucial source of information for the further regulatory procedure.

On principle the idea of involving patients in such processes is not new. As early as 2004 involvement of patient organisations in the shaping of the national health system became statutory. Accordingly it is stated in the Code of Social Law (SGB): “The organisations decisively committed to the safeguarding of patients’ interests and the self-help groups of chronically ill and handicapped persons, shall be involved in all issues relating to patient care (...).“

Therefore, the organisations who prominently represent at federal level the interests of patients and self-help groups of chronically ill and handicapped people in Germany, are involved in the decision-taking process of the Federal Joint Committee (G-BA). Currently these organisations are the German Disability Council (DBR), the Federal Working Committee of Patient Contact Centres (BAGP), the German Working Committee of Self-help Groups (DAG SHG), and the Federation of German Consumer Organisations (VZBV). They can notify experts to join the discussions and deliberations in the relevant committees. Yet, involvement of these organisations in the licensing agencies is not statutory.

However, as a partner of patients the BfArM is anxious to intensify cooperation with these organisations. “We want to establish an intensive exchange and transparent communication to advance the work of both sides“, underlines Broich.

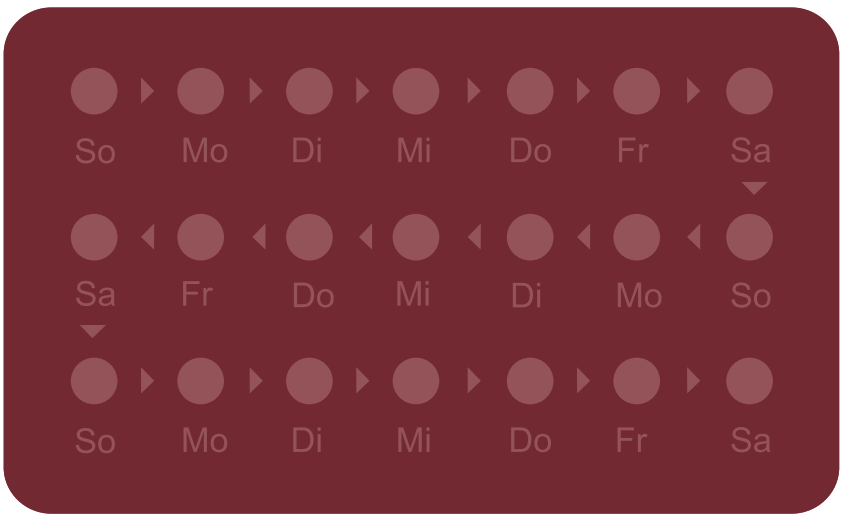
Patient representatives are already involved in G-BA activities. What is decided there has immediate consequences for more than 70 million people in the statutory health insurance in Germany. G-BA decisions depend, among others, on the scientific advice provided by the BfArM. So also at this level the dialogue between the licensing authority and the patient organisations can be beneficial to both sides.

Further possibilities of cooperation are currently under discussion. The first meetings at the BfArM in Bonn have been favourably evaluated by members of the organisations. Optimistic feedback came from them when the two licensing agencies, BfArM and PEI, signalled their will to extend the cooperation. In a further step our plans and ideas shall take a more concrete shape. The BfArM and the PEI have stated that they would encourage the involvement of representatives in the European bodies, as and when required. Both agencies, together with experts from the other European licensing agencies, are engaged in the scientific work of all decisive bodies of the European Medicines Agency. "We have deliberately taken up the growing demand for information to make progress in our mutual exchange to the benefit of patients", says Broich. "The response shows us that we have raised an important issue, which will produce an additional value for both sides in view of future developments."

*"The patients' expectations are of increasing relevance to regulatory decisions. They play a key role in the implementation and optimisation of treatment strategies and they can even stimulate new procedures. "*
***Prof. Dr. Karl Broich,***
***President of the BfArM***

# Selection of appropriate contraceptive: Mind the Risk of Thrombosis

BfArM recommends prescription of combined hormonal contraceptives with the lowest risk of venous thromboembolism especially to first users and users below the age of 30.




Venous thromboembolism is a well-known rare adverse reaction to hormonal contraceptives, the so-called combined hormonal contraceptives (CHC), consisting of a progestogen and an estrogen. For many years the BfArM has pointed out the increased risk of venous thromboembolism due to hormonal contraceptives. The BfArM appeals to doctors to carefully counsel women on the risk of thrombosis associated with the many authorised pills and to consider all additional individual risk factors.

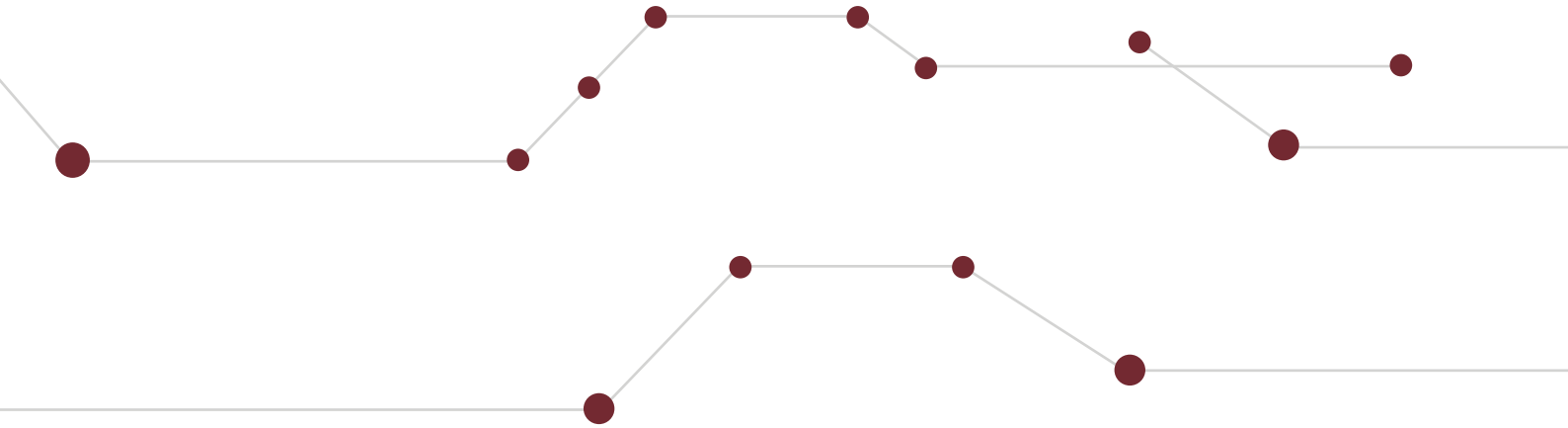
The lawsuit of a patient against a pharmaceutical company has led to new public discussions about the risk of thrombosis in connection with the pill. In the focus is a combination pill containing the active substances drospirenone (the progestogen component) and ethinyl estradiol (the estrogen component).

The risks caused by contraceptives containing the female sex hormones (progestogens) drospirenone and levonorgestrel were already compared with each other in two studies dating back to 2011 (Jick et al. 2011, Parkin et al. 2011, Twofold increase in the risk of thrombosis confirmed by the re-analysis, conducted on behalf of EMA in 2011, of new data in a Danish cohort study by Lidegaard et

al. 2009). The outcome of the comparison showed that the risk of thrombosis is up to twice as high for drospirenone-containing pills as for levonorgestrel. As a consequence, the patient package leaflet for drospirenone-containing pills has been updated accordingly, i. e. information has been added on the increased risk of thrombosis under drospirenone.

Already in the past the BfArM argued that beside the individual risks, the risk of venous thromboembolism should be the decisive selection criterion in the prescription of an appropriate preparation. In 2013 the BfArM, in co-operation with the other European authorities and the European Medicines Agency (EMA), re-assessed the benefit-risk ratio for combined contraceptives. All medicinal products authorised in the European Union for use as combined hormonal contraceptives were investigated. The outcome of the investigation demonstrated that the benefit outweighs the risks in all CHCs. However, there are substantial differences in the risk of thrombosis, depending on the progestogen contained in a product. The smallest risk was seen in pills containing the progestogen levonorgestrel (see Table). Therefore the BfArM recommends the prescription of the CHC with the lowest risk of venous thromboembolism, especially to first users and users below the age of 30 (levonorgestrel-containing CHC). Doctors have the important task to inform the women carefully about the differences in the frequency of occurrence of venous thromboembolism associated with the different products authorised (depending on the progestogen contained in the products). Before a pill is prescribed it is necessary for doctors to tell the women how to recognise the signs of a thrombosis. Also the personal risk factors, which can additionally increase the risk of venous thromboembolism, like smoking or overweight, should be discussed in detail with each patient before prescribing her a pill.

In 2014 a Dear Doctor Letter was written and circulated, in cooperation with the BfArM; as were a check list for doctors and an information sheet for patients. The latter should be given to the patient by the doctor when making a new prescription. It provides important information on the risk of thromboembolism and explains how patients can recognise a thrombosis by themselves. Doctors are urged to pay more attention to the different risks when prescribing contraceptives and to inform their patients better about the substantial differences



in contraceptives especially with regard to the risk of developing a thrombosis. Guidance by doctors is of particular importance when young first users are determined to be prescribed a specific contraceptive without being informed about the related risks. In such cases it is necessary to make clear to them that contraceptives are medicinal products associated with risks, and that they are by no means lifestyle products taken to bring about beautiful skin and hair, weight reduction or a better mood.

All relevant information on the topic is compiled on the BfArM website.
www.bfarm.de/kontrazeptiva

The following table presents the progestogens contained in the various pills including their respective thrombotic risks:

| The risk to suffer venous thrombosis within one year | |
|---|---|
| Women not taking hormonal contraceptives and not pregnant | ca. 2 in 10,000 women |
| Women taking CHC containing levonorgestrel, norethisterone or norgestimate | ca. 5-7 in 10,000 women |
| Women taking CHC containing etonogestrel or norelgestromin | ca. 6-12 in 10,000 women |
| Women taking CHC containing drospirenone, gestodene or desogestrel | ca. 9-12 in 10,000 women |
| Women taking CHC containing chlormadinone, dienogest or nomegestrel | Not yet known* |

* To be able to evaluate the risk of these products further studies are planned or are ongoing to collect further data

# Re-assessment of Risk: No Codeine to Children

BfArM initiated new risk assessment procedure to implement further risk reducing measures in treatment of cough.

In April 2014 the BfArM initiated a European level re-assessment of the benefit-risk ratio in medicinal products containing codeine. Already in 2013 the use of these products for pain therapy in children was strongly restricted when fatal and life-threatening cases were reported of respiratory depression (shallow or lowered breathing). Now the BfArM wanted to achieve risk reducing measures also for the treatment of cough.

Codeine is a well-known substance used for decades in the treatment of pain and dry cough. Codeine action is triggered by an endogenous enzyme that converts codeine to morphine. In five to ten per cent of the European population this enzyme is genetically changed: enzyme activity is insufficient with the result that no pain-killing effect of codeine is achieved in these individuals, the so-called poor metabolisers. By contrast, in ultra rapid metabolisers activity of this enzyme is very high so that codeine is converted to morphine more rapidly and in larger amounts. The genetically changed forms of the enzyme are also responsible for differences in the metabolism of other medicinal products, for instance of anti-depressants. From January 1978 to August 2012 one death case in childhood due to co-

There are genetic differences in the metabolism of medicines. While about three per cent of our population are genetically caused ultra rapid metabolisers of medicines, these about 10 per cent in Southern Europe and up to 30 per cent in Ethiopia and in some Arab countries.

deine was reported to the BfArM from Germany. Also other countries reported fatal or life-threatening cases in connection with codeine. It turned out that the affected children were ultra rapid metabolisers. In their bodies the codeine had been metabolised very rapidly, which led to serious adverse drug reactions like restricted breathing and even death. Since no quick tests are available for checking the genetic disposition it cannot be predicted how patients will metabolise the codeine they receive. In order to examine the benefit-risk ratio also for the treatment of cough on the European level the BfArM initiated a risk assessment procedure in 2014. As a result, the competent bodies in the European Medicines Agency decided that codeine was no longer allowed to be administered to children below 12 years of age. It was further ruled that liquid medicinal products containing codeine were to be dispensed now in child resistant containers to avoid medication errors and faulty administration (e.g. overdoses).

The BfArM is generally concerned with the question of how to improve the identification of drug related risks and how to adjust therapies individually. Therefore pharmacogenomics and personalised medicine have become a research issue of high priority at the BfArM.

We want to obtain new information about individual differences in response and tolerance to various medicines, from the molecular basis through to the clinical level. This shall help us improve risk identification and enable individual therapy adjustment. If we manage to achieve a more efficient adjustment of therapies to the special characteristics of patients this will be a contribution to future personalised medicine.

# Study Analyses Adverse Drug Reactions

Outcome of ADRED study contributes to improvements in drug therapy safety for patients.


ADRED
Versorgungsforschung
für Arzneimittelsicherheit

Adverse drug reactions (ADR) are considered by the general public and the professional community to be an important health problem as well as an economic issue. According to estimates a remarkable percentage of annual emergency admissions to hospital is caused by ADR. There are, however, remarkable deviations in statements about the involvement of medication errors and about frequencies and causes. Therefore, in 2015 the BfArM initiated the ADRED study. ADRED stands for Adverse Drug Reactions in Emergency Departments.

In the ADRED study the causes of serious ADR, first of all medication errors, are analysed and more precise data are collected on frequency and case development. Types of errors are classified and their frequencies determined on the level of the medication process chain. Another focus of the study is the recording and evaluation of patient dependent risk factors for ADR. These are, for instance, age and concomitant diseases, concomitant consumption of various medicinal products, and pharmacogenetics. In order to demonstrate the economic relevance of the problem, a pharmacoeconomic analysis is performed.

Gefördert durch:

Bundesministerium
für Gesundheit

aufgrund eines Beschlusses
des Deutschen Bundestages

In the framework of the ADRED study, three central emergency departments in hospitals providing priority and maximum care will prospectively include, for one year, all suspected cases of serious ADR that have prompted emergency admission of the patients. Each of the suspected cases is followed up and documented throughout the time of hospitalisation. We assume that at least 9000 ADR cases can be recruited for this case development cohort.

The systematic investigation of the potential causes of ADR in the framework of this study will be the basis for developing preventive measures. The results of the ADRED study will contribute to improvements in drug therapy safety for patients.

The project is performed in close cooperation with the Drug Commission of the German Medical Association (AkdÄ), who are simultaneously concerned with a project for the central recording and evaluation of medication errors. Their project also includes data from the spontaneous reporting system, i. e. suspected cases reported, among others, by doctors and patients. Both projects are sponsored by means of the action plan of the Federal Ministry of Health for the improvement of drug therapy safety in Germany.

Pharmaceutical companies are obliged to record and evaluate any known adverse drug reactions and label them in the summary of product characteristics. Also the health care professionals are legally obliged to report any ADR, for the benefit of higher therapy safety.

The BfArM provides online access to its data base of reports of suspected ADR. This new on-line service is another possibility for physicians and patients to obtain better information on drug related risks.
http://nebenwirkung.bfarm.de

# Personalised Medicine for Space Missions

Pharmacogenomics and personalised pharmacotherapy is a research priority at the BfArM. Efforts are aimed at preventing serious adverse reactions wherever possible – something of great relevance also to the ISS crew.

*Picture: NASA*

While the majority of people tolerate a medicinal product well the same product may trigger serious adverse reactions in others. The occurrence of adverse drug reactions should be prevented wherever possible. Also for the crew of the International Space Station (ISS) adverse drug reactions may have fatal consequences. In order to prevent such reactions we should be able to predict them. The BfArM, the University of Bonn, and the European Space Agency took up the issue and pursued the question: What can pharmacogenetic diagnostics contribute to space missions?

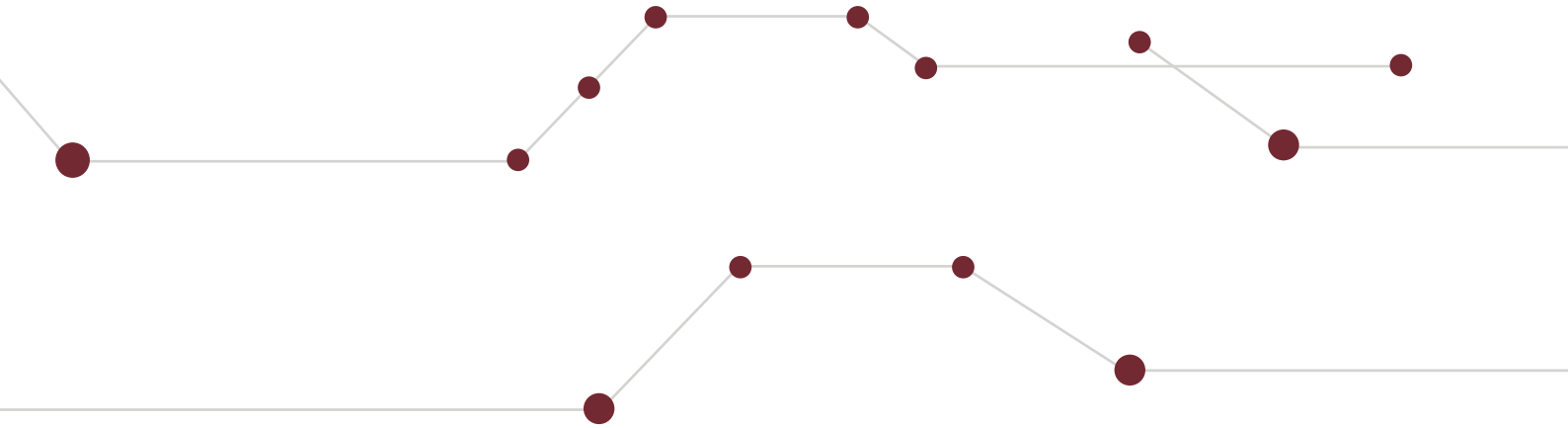
How patients react to a medicinal product is also a question of their genetic predisposition. About three per cent of our population belong to the so-called ultra rapid metabolisers. This means that they metabolise active substances of medicinal products much more rapidly than the majority of people do. As a result they have a higher risk of adverse drug reactions or of failing therapeutic effects. The opposite are the so-called poor metabolisers. They metabolise active substances more slowly than most people do. Also in them certain agents do not generate the wanted effects. Their risk is that the active substance level in their blood is high for too long or that it persists at a high

level. Such a state can also provoke serious adverse reactions. The percentage of the different types of metaboliser varies: for instance, about 10 per cent of the population in Southern Europe and up to 30 per cent in Ethiopia and some Arab countries are ultra rapid metabolisers.

Owing to this phenomenon, the BfArM has made pharmacogenomics and personalised medicine a research priority. The research group headed by Prof. Dr. Julia Stingl investigate the individually based differences in drug action due to inborn genetic differences. Their investigations are aimed at improving the recognition of risks and at adapting therapies to individual needs. Pharmacogenetic tests show how a patient metabolises medicinal products. The decisive factors are certain liver enzymes. About a quarter of all medicinal products are metabolised by two liver enzymes, enzyme CYP2D6 and enzyme CYP2C19. Genetically induced modifications to the activity of these enzymes, either reduced or increased activity, lead to the described variations in metabolism.

Against this background the BfArM looked through the list of the 78 medicinal products that were available on board the ISS in 2014. The range of medicinal products found there is interesting in so far as the products are representative of the typical medication for basically healthy people. The

The BfArM looked through the list of the 78 medicinal products that were available on board the ISS in 2014. The range of medicinal products found there is interesting in so far as the products are representative of the typical medication for basically healthy people.



products provisioned at the ISS are mainly agents to treat infection, pain and inflammation, nausea and allergies, followed by products against diseases of the gastrointestinal tract and against high blood pressure. The ISS has another particularity in store for pharmacogenetics: the international origin of the crew reflects the wide genetic variability among drug users. So the pharmacogenetics of the ISS pharmacy can be understood as a compendium illustrating the impact of the genetic variability in people coming from an international environment.

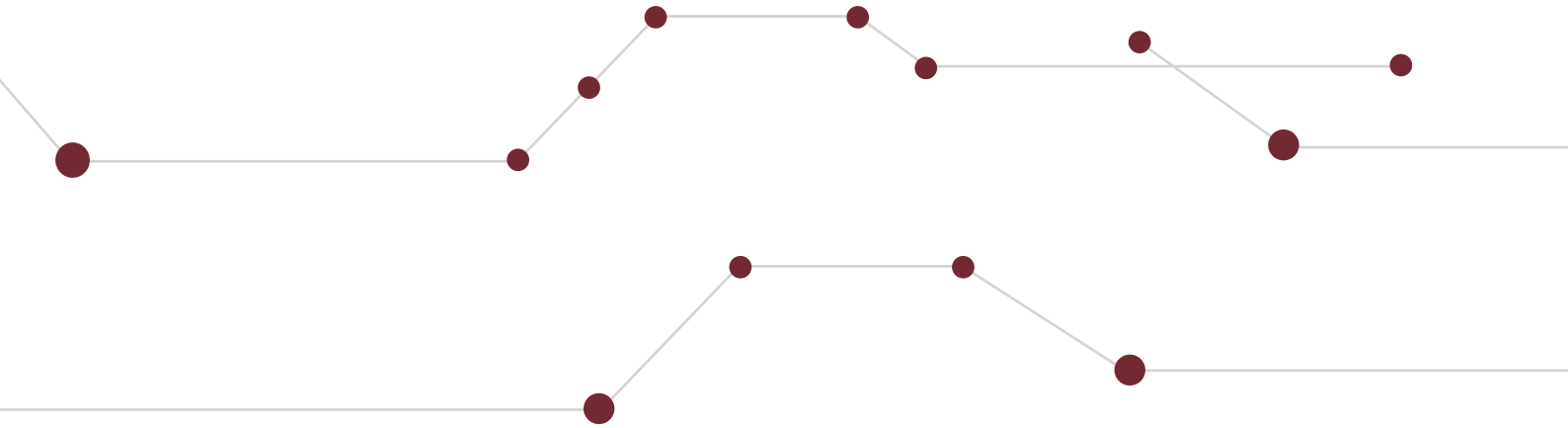
In so far the investigation has also shown how pharmacogenetic risks appear in normal consumers taking the normally available medicinal products.

# Pain and Palliative Medicine: Permanent Learning Process

The Federal Opium Agency is building basic structures of a competence centre for pain and palliative medicine with the focus on narcotic drug supply.

One of the main tasks of the Federal Opium Agency is the control of the legal narcotic drug market. Customers are under the impression that the Agency regulates the market very tightly. This impression is due to the fact that in the narcotic drug market everything is principally forbidden unless explicitly permitted by the authorities. The Agency supports the safe handling of narcotic drugs in industry and trade by setting clear-cut rules, by providing extensive individual counselling, and by satisfying practical demands in an unbureaucratic way as far as compatible with the statutory specifications.

The Federal Opium Agency guarantees that patients are safely supplied with the medically necessary narcotic drugs. 14 million prescription forms are distributed every year to physicians who must use these special forms for the prescription of narcotic drugs. The Agency is in charge of authorising the import of narcotic drugs and monitoring their pathways from manufacture via wholesale trade to the pharmacies. Inspections ensure that the statutory narcotic drug provisions are complied with so that the products reach patients safely and diversion of drugs for abuse is excluded as far as possible. “Supply of narcotic drugs is no static process“, states Dr. Peter Crem-

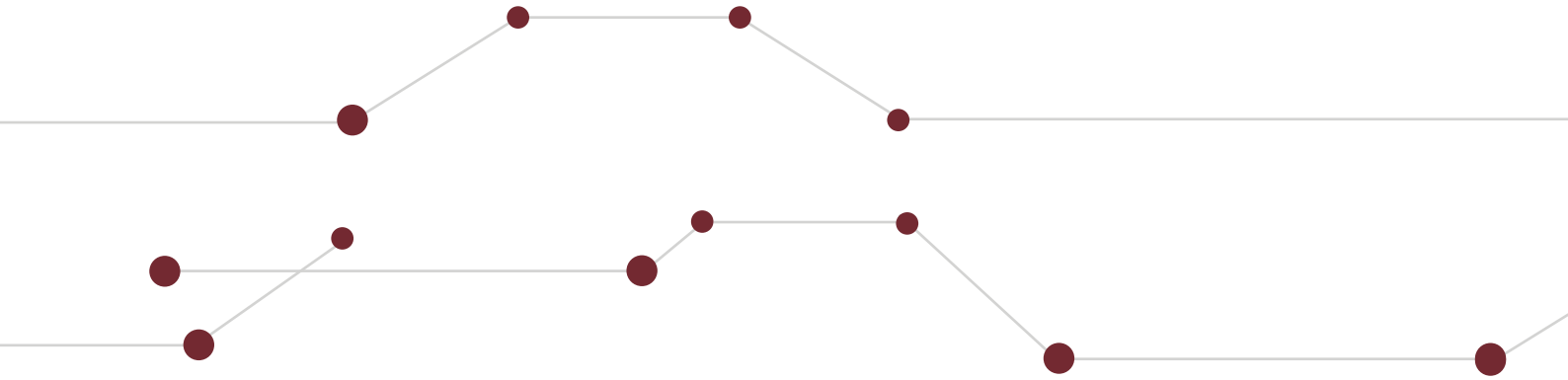


*"The Federal Opium Agency is anxious to respond to the needs and issues raised by the health care system in connection with the supply of narcotic drugs, and to develop pragmatic solutions."*
***Dr. Peter Cremer-Schaeffer, Head of Federal Opium Agency***

er-Schaeffer, Head of Federal Opium Agency. "The Federal Opium Agency is anxious to respond to the needs and issues raised by the health care system in connection with the supply of narcotic drugs, and to develop pragmatic solutions." This includes counselling of the Federal Government in the process of amending the narcotic drug provisions. We are aiming to adjust the narcotic drug supply to the needs of patients in a changing society with changed supply structures.

The Federal Opium Agency can only manage to improve the drug supply to patients if it cross-links with the service providers in the health care system and learn permanently more about the needs of the patients. The Agency is now confronted with a lot of issues which did not play a role in the supply of narcotic drugs ten years ago. The following examples are only some of the topics that will influence the narcotic drug supply: further improvements in palliative medicine and pain therapy, dropping numbers of physicians performing substitution therapies, the demographic change, new challenges in the emergency service, the further urbanisation of our society. Our learning must become a permanent process, and the changing conditions should be given due consideration in planning future staff requirements. Therefore the Agency will staff a project post, currently limited to a period of four years, to be concerned with establishing the basic structures of a competence centre for pain and palliative medicine under the regulatory conditions.

The project will focus on three key aspects: Firstly, evaluation of all the knowledge already available at the BfArM on narcotic drug supply, involving all the divisions that have to do with the subject matter in some way or other, i. e. the authorisation and pharmacovigilance divisions as well as the Federal Opium Agency itself, the Clinical Trials unit and the related Legal Affairs unit. Secondly, intensification of contacts with those medical societies who are permanently concerned with the use of narcotic drugs, i. e. pain therapy, palliative medicine, substitution medicine, anesthesiology, intensive medicine and the emergency medical services. Thirdly, reviewing the supply data that have already been collected but not yet evaluated at the BfArM, mainly data of the Federal Opium Agency itself. These data could be included in the narcotics supply research in the medium-term.



Provided the project is successfully completed we plan to establish a permanent competence centre for pain and palliative medicine at the BfArM with the focus on narcotic drug supply.

# Medical Devices: New Methods of Risk Identification

A special software for improved evaluation of large data volumes is developed by BfArM together with industry and research.


The BfArM research group Safety of Medical Devices under the supervision of Dr. Wolfgang Lauer has raised funds for a period of two years for the development of a risk identification software. Six partners from research and industry will be involved in the software development. The aim is to design new methods for the systematic exploitation and evaluation of large data volumes, as are available in scientific publications on medical technologies, in administrative or public data bases. The new methods shall be used to support post market surveillance of medical devices. The project is sponsored by the Federal Ministry of Education and Research in the framework of the support programme KMU-innovativ/IKT (identification number 01IS15056G).

The evaluation of the data is based on the so-called ontologies. This means that concepts and their interrelations are prepared in such a way that the software is able to process the data and combine them meaningfully in complex data mining processes. The specific challenge is the generation of algorithms that are able to transfer the risk related information found in free texts, into structured data and to analyse them. The project is called “OntoPMS“ - a combination of ‘ontology’ and the post market surveillance acronym ‘PMS’. The

scientific sub-projects under the roof of “OntoPMS“ at the BfArM are supervised by Dr. Robin Seidel.

The BfArM research group has already developed first steps towards better data evaluation, as for instance the data on medical device incidents. The current project and the close cooperation with research and industry partners will improve our potential for testing and evaluating such first scientific steps in practical applications. Besides, these first attempts shall be developed to make them fit for use in the regulatory risk assessment of medical devices at the BfArM. The aim is to improve the identification of technical and medical risks associated with certain materials, design characteristics or application areas of medical devices. Also the identification of risks that occur with similar devices of similar characteristics (e.g. batteries, insulation compounds) is to be improved. Efforts are focussed on cross product analysis and practically oriented data editing. In this way the BfArM wants to develop new methods of data analysis so that in the future the existing risks of product groups can be characterised more efficiently and potential defects of medical devices detected earlier.

New concepts for a practically oriented, graphic and easily comprehensible representation of the obtained risk information shall be designed and tested in the project. Such a software gives manufacturers of medical devices a better tool for risk identification and risk minimisation, both in existing devices and further developments alike. Such improvements are also in the direct interest of the BfArM and the other national and European agencies.

GEFÖRDERT VOM

Bundesministerium
für Bildung
und Forschung

*The project is sponsored by the Federal Ministry of Education and Research in the framework of the support programme KMU-innovativ/IKT (identification number 01IS15056G).*

***Project partners:***
*Institute for Medical Computer Science, Statistics and Epidemiology at the University of Leipzig, IntraFind Software AG, MT2IT GmbH & Co. KG, novineon Healthcare Technology Partners GmbH, OntoPort UG, Ovesco Endoscopy AG*

# Improving Access to Pharmacogenetic Diagnostics

Implementation of procedures for personalised medicine is an important element in the improvement of drug safety.

*Prof. Dr. Julia Stingl*
*Vice President of the BfArM*

Since 2014 all activities supporting and encouraging research and innovation in the EU have been concentrated under "Horizon 2020", the biggest funding programme ever launched in the European Union. One of the research priorities in the programme is the implementation of procedures for personalised medicine. Personalised medicine has the potential to contribute to better drug safety for patients by applying methods of pharmacogenetic diagnostics, this means that drug therapies are individually adjusted and that pharmacogenetically based dosing concepts are used to the advantage of the patients. The main purpose is the decrease in the number and the seriousness of adverse drug reactions.

The establishment of the BfArM research department by Prof. Dr. Julia Stingl makes it possible for our institute to participate in large European joint research projects. The EU-funded U-PGx study (Ubiquitous Pharmacogenomics): Piloting personalised medicine in health and care systems, launched in January 2016, is designed to make access to pharmacogenetic diagnostics, as an instrument of personalised medicine, easier for patients across the EU. The study conducted at large university hospitals in seven European coun-

tries aims to increase drug therapy safety by pharmacogenetic testing of patients. The EU supports the study, which is planned for a period of five years, by contributing €15 million. Prof. Julia Stingl is a partner in the consortium of 16 members, which is coordinated by Prof. Dr. Henk-Jan Guchelaar from the University of Leiden.

**Prof. Stingl, what is the aim of the research project at the BfArM?**

We aim to increase drug therapy safety by using pharmacogenetic diagnostics and individually tailored dosing schemes. The study is to investigate whether individualised risk information that integrates the pharmacogenetic characteristics of patients, is able to increase the safety of drug therapies. Seven clinical centres across Europe will be investigating whether pharmacogenetic therapy information provided routinely to attending physicians, can help decrease the number and the seriousness of adverse drug reactions in a hospital. In each of the participating hospitals an 18 month period of conventional prescription practice will be compared with an 18 month period of pharmacogenetic diagnostics. In the pharmacogenetics phase, physicians and hospital pharmacists will undergo courses to learn what they need to know about individual drug risks and the potential of pharmacogenetic diagnostics in daily clinical routine.

In 2014 the EU-funding programme "Horizon 2020" was launched with a budget of nearly € 80 billion, thus the biggest European research programme ever. A focal point is the better networking of researchers and the chances of research stays in other countries.

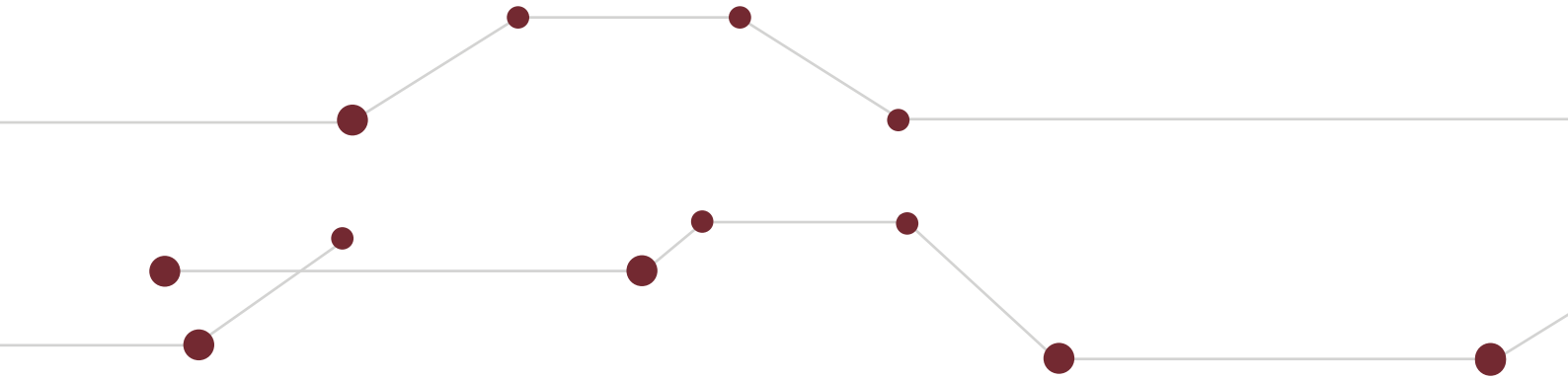

*U-PGx project granted by the EU H2020 programme (grant°668353).*

**What exactly is the potential of pharmacogenetics?**

We have already got various possibilities to tailor drug therapies to patients' genetic predispositions. Admittedly, pharmacogenetic tests have not yet been extensively applied in daily clinical routine. It we can investigated, for instance, whether a systematic gene typing of patients who take a variety of medicines simultaneously, results in safer treatments. If so it would be a contribution to greater drug therapy safety in the long run.

**What does this precisely mean to patients?**

Patients are given information on their individual risk factors for adverse drug reactions. For one patient this could mean that the attending physician prescribes a lower dose, for another patient that an alternative medicinal product is chosen. Also, it will strengthen the awareness in patients that people may



respond differently to medicinal products and that it is important to predict their own responses as precisely as possible to avoid adverse drug reactions.

**What are the advantages of such an approach?**

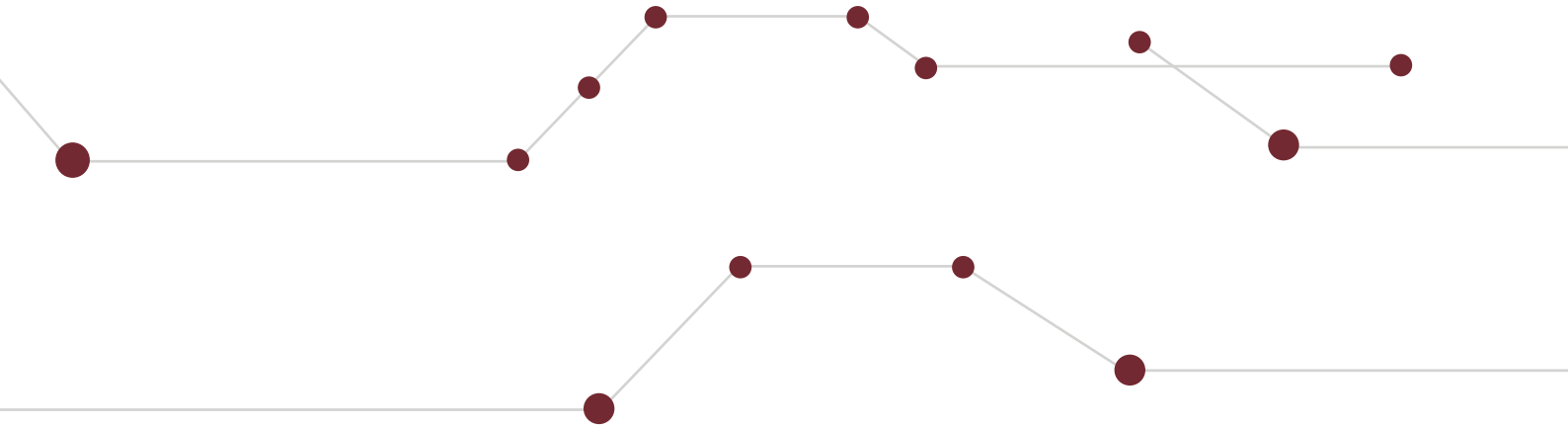
Apart from specific dose adjustments or the selection of the most appropriate medicinal product, such approach strengthens the individual health awareness and can generally enhance the knowledge of drug therapy related risks and side effects. At the same time the investigation of individual risks can help reduce potential uncertainties and anxieties about drug therapies. This may then enhance the readiness of patients for cooperation in their treatment.

**Can we anticipate that pharmacogenetic diagnostics will be the future standard in drug therapy?**

Let me state that we are talking here about the so-called companion diagnostics, which means that it is not necessary for every patient and every drug therapy. Also in our study this kind of diagnostics is applied only concomitantly in those cases of drug therapy where therapy adjustment according to a given genotype is recommended. A standardised approach allows us, on the one hand, to reduce less efficacious drug therapies and, on the other hand, to reduce the occurrence of undesired side effects. Thereby we can also avoid certain cost factors, i.e. costs that may be incurred by diagnostic and therapeutic measures necessary to combat resulting serious adverse drug reactions.

**What are the tasks for the BfArM scientists in this research project?**

Our part in the project is mainly that of ascertaining the level of pharmacogenetic knowledge among physicians and patients. We will shed light on the differences in the level of knowledge across the participating European countries. As for the patients, we will first of all look into their attitudes towards drug therapy and personalised medicine and point out the differences within the



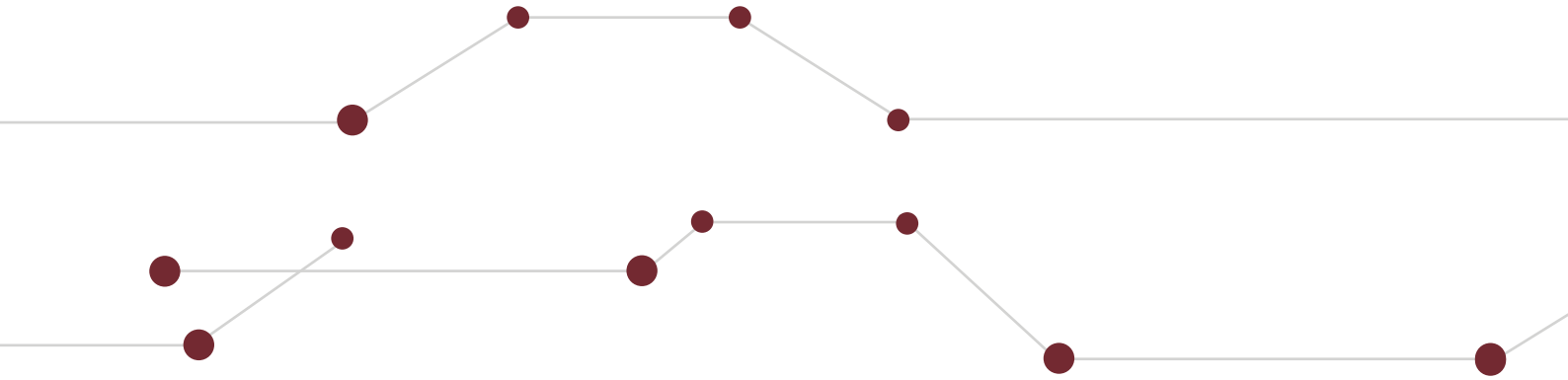
European countries. We will examine whether patients who metabolise medicinal products slowly and may have repeatedly had the experience that they do not tolerate the medicines well, have developed a different attitude towards drug therapies from those patients who consume a lot of medicinal products simultaneously yet have hardly ever suffered adverse reactions even if on high doses. Further, in order to raise the knowledge about personalised treatment among patients and in the general public a video film about personalised medicine will be produced.

**The research department is expected to provide the scientific basis for the regulatory tasks of the BfArM and to improve health care for and safety of the population. How far does participation in the study comply with these tasks?**

The study complies fully with these tasks. Its aim is the increase in patient safety by avoiding adverse drug reactions and making use of up-to-date pharmacogenetic test methods. These methods are of great importance also for the development of new medicinal products. An increasing number of newly developed medicinal products is placed on the market with the specific recommendation for use in pharmacogenetic companion diagnostics. This includes many important indications, such as new therapeutic approaches in cancer medicine. Thus the study does not only contribute to increasing patient safety, but supports the BfArM in performing their regulatory tasks in the framework of drug authorisation and pharmacovigilance.

**Personalised medicine is becoming ever more important in our health care system. What is the part of the BfArM in this development?**

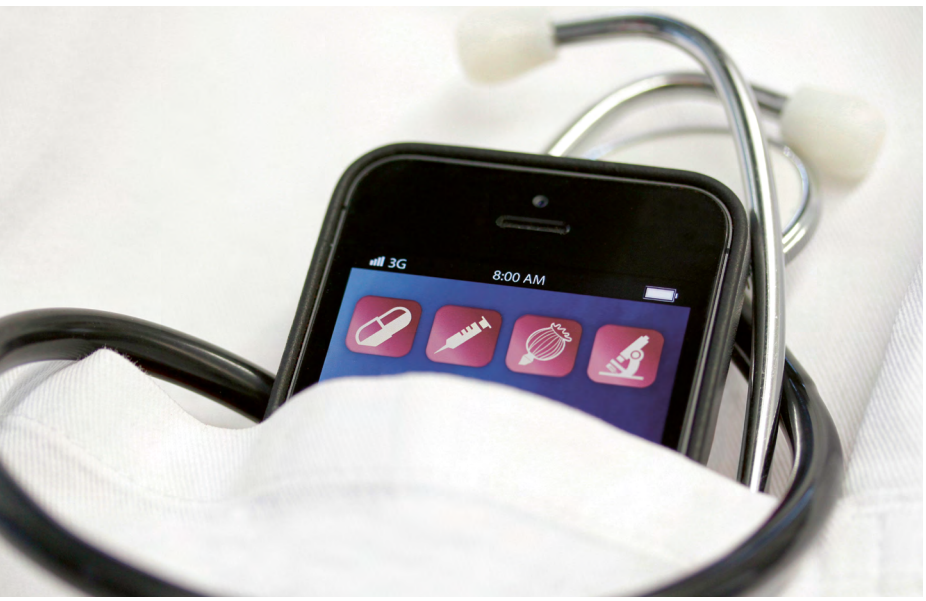
In the field of pharmacogenetics the research department conducts molecular investigations into the variability of the benefit-risk profile in drug therapies; the research results are published in high-ranking international journals. Our research department is a leading participant in German and European joint research projects and has raised third-party funds from public funding



organisations in highly competitive processes. The current BfArM projects investigating drug therapy safety in cases of pharmacogenetic particularities, vulnerable patients and individualised therapies, are long-term key research topics providing the scientific basis for the regulatory tasks of the BfArM. The projects are primarily targeted at improving the health care for and safety of the population. Simultaneously they highlight the scientific expertise of the BfArM both in the wide range of international multi-centre tasks and also in the case of specific current issues. Take, for instance, how important it is for our clinical trial unit to have the latest knowledge about biomarkers and biological companion diagnostics – nowadays components in almost every multi-centre study.

# BfArM Provides Guidance for Medical Apps

Where is the borderline between applications for wellness and medical devices? BfArM has dealt with the question.



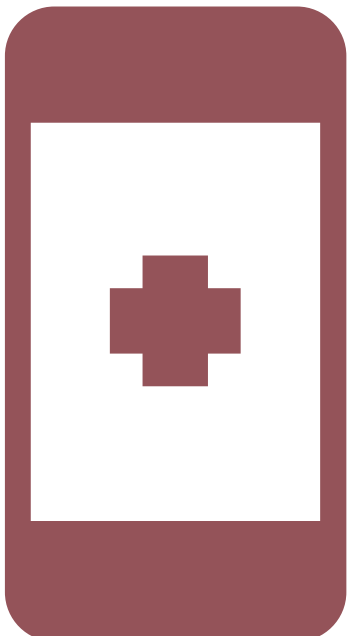

Software applications for mobile phones and tablets, the so-called “apps“ have become our daily companions at work as well as in our spare time. Health related apps have been increasing rapidly in recent years. Apps measure our fitness, give health tips, analyse physiological data and calculate drug doses. Where is the borderline between wellness apps on the one hand and medical devices on the other? The BfArM has dedicated to the question and developed an orientation guide.

The BfArM picked up the topic of “Medical Apps“ proactively in 2015 and again in 2016 at “BfArM im Dialog“ meetings to provide a discussion platform to the many stakeholders. About 200 experts from industry, from research, from politics and administration, took the opportunity to talk about chances and risks of medical apps. “The BfArM sees itself as an impulse transmitter for the benefit of health protection“, says BfArM President, Prof. Dr. Karl Broich. “Consumers must be given the certainty that apps for medical purposes are clearly regulated, reliably tested and reviewed.“
Also for patients software applications for mobile phones and tablets have become daily companions. Health related apps have been increasing rapidly

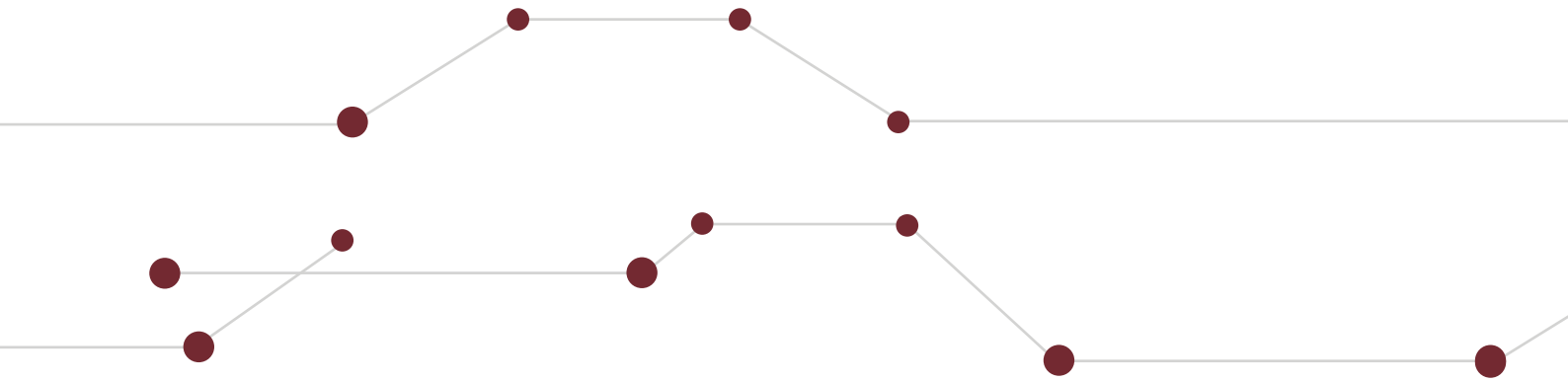
in recent years. The borderline between wellness apps and medical devices is not always apparent. For this reason BfArM has developed an orientation guide. The guide shows whether a product falls within the scope of the Medical Devices Act (MPG) and is subject then to the provisions in this Act; it helps to distinguish wellness apps from medical devices and explains the risk classification as defined by the MPG.

Using apps may pose risks, especially where they are utilised for diagnostic and therapeutic decisions, such as diagnostic imaging, image interpretation of carcinoma, or calculation of drug doses. Medical devices are subject to clearly defined regulations for safety, quality and monitoring. Users must rely on their proper functioning, must be certain that calculations, say, of insulin doses are correct. Wellness apps, however, are not subject to similar regulations. So there are app suppliers who try to evade the regulations by labelling their products as non-medical-device. But such a non-medical device label is invalid as soon as a medical function is earmarked for the app. The general rule is: apps are considered to have medical device qualities if they are supposed to be used for a medical purpose and if in a health care facility, medical data bases and algorithms are combined with patient specific data, and if the software is designed for the purpose of giving medical professionals recommendations as to the diagnosis, prognosis, monitoring or treatment of an individual patient.

The orientation guide shows whether a product falls within the scope of the Medical Devices Act and is subject to the provisions in this Act.



Whether a product is a medical device or not is first of all decided by the manufacturer or his/her authorised representative, in cooperation with a notified body or the Federal State Authorities if applicable. The decisive criterion is the purpose of the product as follows from its labelling, instruction for use, and advertising material. There are cases where the BfArM decides, upon request, on the demarcation and classification of specific medical devices. Persons entitled to make such a request to the BfArM are manufacturers of medical devices, and the Federal State Authorities for the manufacturer in question, as well as notified bodies, the latter only in cases of disagreement between manufacturer and notified body.



## Background: Medical Devices

**Marketing and the regulations for access to the market**

Medical devices are appliances, instruments or other articles with a medical purpose intended by the manufacturer to be used for human beings and applied in medicine. They act on the body (plaster, blood pressure meter, etc.) or in the body (artificial hip joints, heart pacemakers, etc.) without interfering with the patient's metabolism as medicinal products do. Unlike medicinal products, medical devices are not authorised by the BfArM or another state authority on the basis of authorisation procedures. Medical devices pass through so-called conformity assessment procedures. In such procedures, which are equivalent to drug authorisation procedures, the manufacturer is required to prove that the product is safe and fulfilling the technical and medical performances as are described by him. Depending on the risk class a medical device is assessed to belong to, a review and certification body is to be involved. These bodies are notified by state authorities, hence called "notified body".

**Tasks of the BfArM in connection with medical device risks**

If safety problems arise with medical devices already on the market and a device fault is suspected to be the cause of a death case or a severe decrease in a person's health, the BfArM will be concerned with the risk assessment of the device involved. If it is concluded that for safety reasons modifications are necessary to the device or to the corrective measures the manufacturer has carried out or planned to do in his responsibility for the device, then the BfArM will issue a recommendation to the manufacturer and to the monitoring authorities of the laender, in accordance with the law and as far as necessary. The Federal State Authorities are competent and legally in the position to monitor these recommendations or to order their implementation in case the manufacturer does not implement them in his own responsibility.

# Pyrrolizidine Alkaloids: BfArM Makes New Requirements

New measures have been taken to protect patients more efficiently from contamination of herbal medicinal products with pyrrolizidine alkaloids.

In Germany the environment for medicinal products belonging to the particular therapeutic systems (phytotherapy, homeopathy and anthroposophy) is a very special one. In the Medicinal Products Act (AMG) these products were intentionally given due consideration as a contribution to the plurality of therapeutic possibilities. They generally enjoy great consumer acceptance. Hence, the BfArM has got a separate division dealing with the procedures and tasks resulting from their authorisation and registration. The division is actively engaged in the pharmaceutical harmonisation in Europe and in the global discussions on the use of traditional medicinal products. It is important to the BfArM that the evaluation of quality, safety and efficacy allows for the appropriate availability of these medicines, but that limits to their application are set where necessary.

The BfArM has taken further measures to protect patients more efficiently from contamination of herbal medicines with pyrrolizidine alkaloids. Pyrrolizidine alkaloids are a group of naturally occurring substances which may be hepatotoxic, i. e. damaging to the liver. They are produced in a complex biosynthetic pathway and are frequently found in certain plant families, such as Asteraceae (composites) or Boraginaceae (borage leaf).

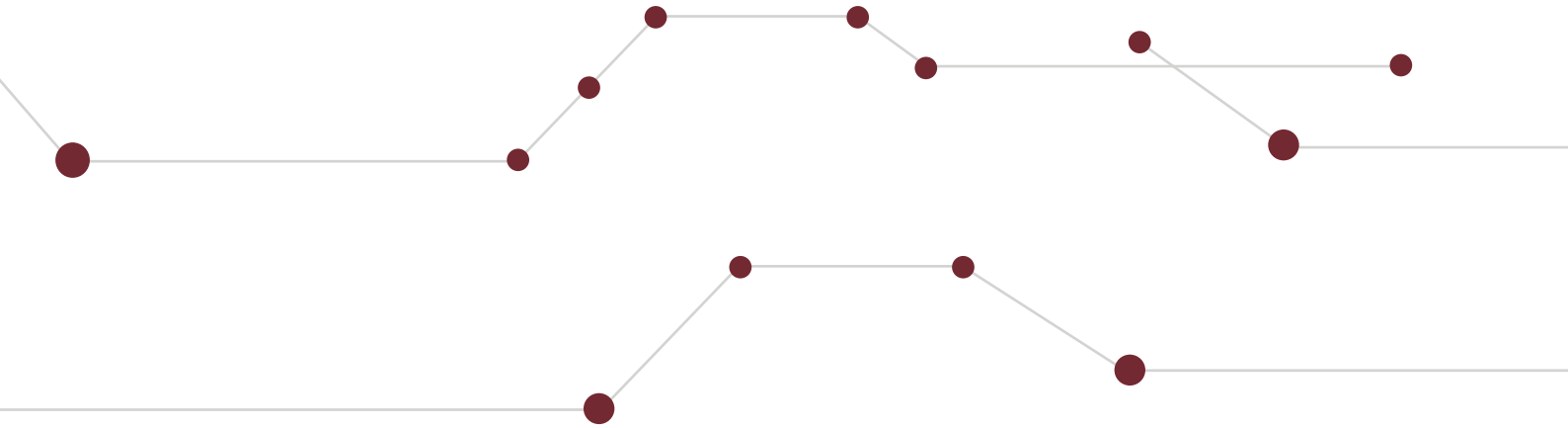
Pyrrolizidine alkaloids are a group of naturally occurring substances which may be hepatotoxic, i. e. damaging to the liver. They are produced in a complex biosynthetic pathway and are frequently found in certain plant families.

For this reason the BfArM has defined requirements for test scenarios and limits to be complied with by the pharmaceutical industry in product quality assurance. The aim is to minimize the presence of pyrrolizidine alkaloids in herbal, in traditional herbal, in homeopathic and in anthroposophic medicinal products. At the same time it is important to ensure the availability of those medicinal products that are not concerned by the contamination problem.

The topic is far from being new: as early as 1992 the BfArM issued a graduated plan procedure specifying a limit for products with active substances containing pyrrolizidine alkaloids. Among them are plant preparations from coltsfoot (Tussilago farfara) and comfrey (Symphytum officinalis).

In the recent years it has become possible by use of improved analytical techniques to provide evidence that also such plants may be concerned which are not capable by themselves of biosynthesizing pyrrolizidine alkaloids. In 2013 the Federal Institute for Risk Assessment (BfR) published data showing that pyrrolizidine alkaloids were detected in some herbal teas. Most of the sample in the BfR analysis came from the food area, but a few samples of medicinal teas were also contained. The detection of pyrrolizidine alkaloids came as a surprise since the plants of the analyzed tea samples were not able by nature to biosynthesize pyrrolizidine alkaloids. Scientifically speaking it was not possible that such plants as chamomile or St John's wort had all of a sudden gained the ability to biosynthesize pyrrolizidine alkaloids; and so it was suspected that it was a matter of contamination.

"We followed the issue critically from the very beginning", states Prof. Dr. Werner Knöss, Head of Licensing Division 4. "For us this meant to develop measures that would enable us to assure the quality and safety of herbal and traditional herbal medicinal products also in the future." Since the first indications of a risk the BfArM has been in contact with the pharmaceutical associations in Germany (German Medicines Manufacturers' Association and Federal Association of the Pharmaceutical Industry). At that time it was most important for us to estimate the scale of the pyrrolizidine alkaloid contamination before we would be able to take the necessary and appropriate measures. The Associations, in collaboration with the pharmaceutical companies concerned, took



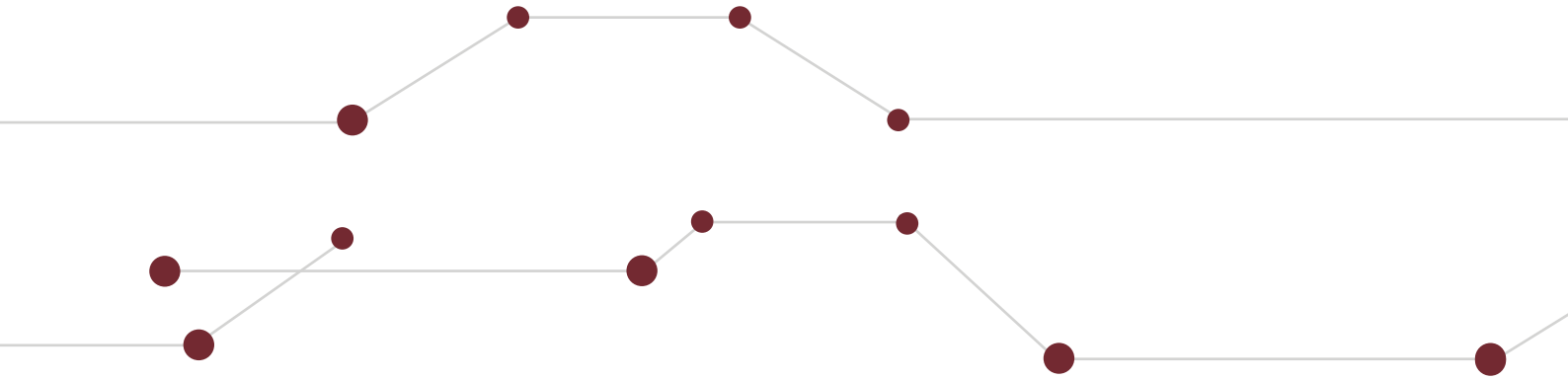
various measures of risk minimization, such as causal research, initiation of GACP projects (GACP: Good Agricultural and Collection Practice), far-reaching testing, and the establishment of a data base. Following talks with the BfArM, the Associations developed a "Code of Practice" that the pharmaceutical companies should meet within the context of their responsibility for minimizing the pyrrolizidine alkaloid content in their products.

*"For us this meant to develop measures that would enable us to assure the quality and safety of herbal and traditional herbal medicinal products also in the future."*
***Prof. Dr. Werner Knöss, Head of Licensing Division 4***

The current investigations suggest that the presence of pyrrolizidine alkaloids is due to contamination with the so-called accessory herbs, such as heliotropic or senecio species, which get into the batches at harvesting. Since the presence of pyrrolizidine alkaloids may be caused by contamination with very few plants, agricultural measures alone will not be sufficient to provide solutions of the contamination problem within a short period of time; it will probably take several years and therefore intensified controls are necessary.

The potential hepatotoxic risks associated with the exposure to pyrrolizidine alkaloids are well-known. They were detailed in the BfArM graduated plan procedure of 1992 (Federal Bulletin No. 111 dated 17 June 1992) and were assessed in a public statement of the Committee on Herbal Medicinal Products (Public statement on the use of herbal medicinal products containing toxic, unsaturated pyrrolizidine alkaloids; EMA/HMPC/893108/2011). Both documents contained limits for the maximum daily exposure, the Public Statement of the HMPC recommended that exposure "should be kept as low as practically achievable". Scientific discussions about limits continue of course, but so far we have no scientifically accepted consistent calculation model taking account of short-term or life-long exposure or including the potential exposure from food consumption. As far as medicinal products are concerned it is uniformly consented that the pyrrolizidine alkaloid content, and thus exposure, should be kept as low as practically achievable.

The BfArM has now defined the measures for minimizing pyrrolizidine alkaloids in herbal, traditional herbal, homeopathic and anthroposophic medicinal products, which the pharmaceutical companies must comply with in quality assurance. All pharmaceutical companies are required to conduct product specific tests of the contamination risk, to determine the pyrrolizidine alkaloid



content and to take the necessary measures. A classification system has been prescribed specifying the volume of testing depending on the contamination risk, and the classification limits. These measures are to guarantee that daily exposure due to medicinal products does not exceed 1 µg per day (following the above-mentioned graduated plan procedure for pyrrolizidine alkaloids of 1992). “This is done to ensure patient safety“, underlines Knöss. The resources should be mainly employed where the risk of contamination is particularly high. Homeopathic preparations from a certain potency scale upwards or products undergoing a certain manufacturing process, may be excluded from the measures if permitted by the available data in accordance with the a. m. graduated plan procedure.

Pyrrolizidine alkaloids were also discussed at a “BfArM im Dialog“ meeting with pharmaceutical companies in April 2016. Also with the other European licensing authorities the BfArM is in contact to discuss about further safety measures. There is urgent need for developing an analytical method for the determination of pyrrolizidine alkaloids to be included in the European Pharmacopoeia. Common strategies for the further approach are devised by the HMPC of the European Medicines Agency. Finally, it remains an important task to maintain the exchange with producers and manufacturers for the benefit of minimizing contamination during crop growing, harvesting and processing, as far as possible.

# More Medicinal Products for Rare Diseases

Increase in orphan drugs is the result of systematic promotion by the EU in combination with general scientific and pharmaceutical progress.

In recent years the development of niche products has become increasingly important for pharmaceutical companies. This is also true for the "medicinal products for rare diseases", the so-called orphan drugs. Designation as orphan drug can be granted by the European Commission to medicinal products developed for the treatment of rare diseases, on condition that the following prerequisites are met: only 5 or even less out of 10,000 individuals are concerned in the EU, the proposed disease is life-threatening or severe, and no or no satisfactory treatment methods are available. Back in 1999 the EU Regulation on orphan medicinal products was adopted granting pharmaceutical companies incentives for the development of preparations for which there exist only small patient groups and as a result only small sales volumes.

The orphan status has no influence on the principal requirements for quality, efficacy and safety of medicinal products. The incentives are of a financial nature and vary depending on the phase of product development. Applications for orphan status are often submitted at an early stage of development. Initially a designation just means that a candidate is identified and given a chance to profit from the incentives for the whole drug development phase.

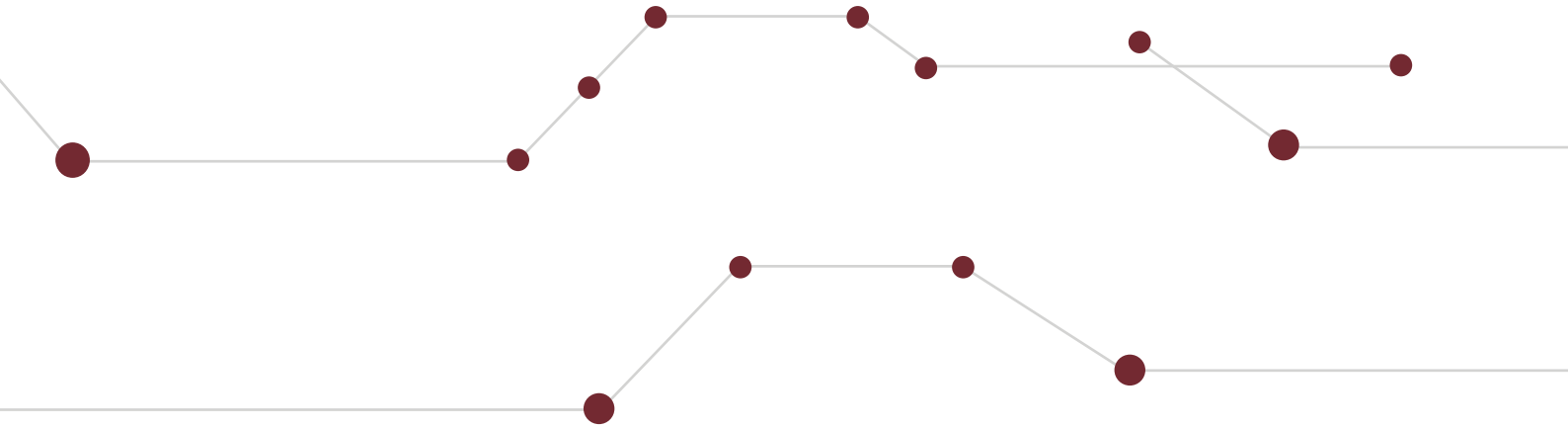
The number of new authorisations for orphan drugs has been growing year after year, with a maximum of 15 new authorisations in 2015. At present 92 medicinal products for rare diseases are authorised in Europe.

Incentives mean that companies developing orphan drugs pay reduced fees for scientific advice; it is hoped that easier access to scientific and regulatory advice stimulates the successful development of orphan drugs. Also the fees for the authorisation itself are reduced.

Often many years pass between orphan designation and authorisation. This is the reason why at the time of authorisation it is checked again whether the orphan criteria are still fulfilled. If the orphan status is confirmed and authorisation i granted, the orphan product enjoys 10 years of market exclusivity in relation to the so-called similar medicinal products. The definition of similar medicinal product includes not only generics but also structurally similar substances with a similar mode of action and similar indication. In the case that the orphan status is not confirmed at authorisation the company is not liable to additional payments but the status of market exclusivity is not granted to them.

The number of new authorisations for orphan drugs has been growing year after year, with a maximum of 15 new authorisations in 2015. This development is the result of the systematic promotion by the EU, and the general progress in science and pharmaceutics. At present 92 medicinal products for rare diseases are authorised in Europe. For more than a dozen of them market exclusivity has expired. Most orphan drugs treat cancer or metabolic diseases, and they are also tested in the typical way, that is in comparative randomised studies, as is the usual case with medicinal products for the more frequent diseases.

Applications for orphan drug status are reviewed in voluntary and charge-free procedures in the Committee for Orphan Medicinal Products (COMP) at the European Medicines Agency (EMA). It is an interdisciplinary committee of clinicians, pharmacists and natural scientists, concerned with the screening and scientific assessment of applications. The COMP include one representative from each Member State of the European Economic Area; further participants are patient representatives and other experts appointed by the European Commission with voting power. The COMP advise the European Commission in the further development of directives and regulations for or-



phan drugs. They maintain international contacts with other authorisation agencies promoting the development of medicinal products for rare diseases, such as the USA and Japan.

The European research programme has adopted the orphan designation procedure in its “Horizon 2020“ programme. Financial support for clinical trials can be requested here if the trial substance has obtained orphan designation and if the applicants have implemented the recommendations given in the scientific advice of the EMA. This possibility has caused a remarkable increase in the number of applications for initial orphan designation to over 250 per year, including applications from academia.

Critics see the growing number of orphan drugs as a result of an ongoing process of splitting the known disease patterns into ever smaller patient subgroups. Dr. Frauke Naumann-Winter, the German representative in the COMP, is aware of the criticism “So far we have granted designation only to medicinal products for clearly defined rare diseases and have not accepted breaking down known diseases into sub-groups according to personalised medicine“, asserts the epidemiologist. This can be demonstrated by the following figures: None of the targeted medicinal products authorised for certain sub-groups of frequent cancer diseases, e. g., of malign melanoma, non-small-cell bronchial carcinoma or breast cancer, had a previous orphan designation in the EU. All in all, in almost three quarters of the diseases for which orphan drugs have been authorised, the number of affected individuals is below 2 out of 10,000 and thus clearly below the regulatory limit. Besides, about one third of the medicinal products with orphan status have been authorised for rare diseases for which no previous treatments had been available so that in these cases the orphan drugs are the first authorised treatments at all.

If authorised therapeutic methods are already available it is necessary to demonstrate that the orphan drug has a significant benefit over the existing one. Only then the orphan drug status can be maintained at authorisation. The significant benefit is defined as “clinically relevant advantage“ or as “major contribution to patient care“. “Clinically relevant” means that the treatment with the orphan drug shows an effect in patients while a previ-

ous treatment had failed to do so. A "major contribution to patient care" is achieved if the orphan product can be administered in the form of a tablet instead of an injection.

"The major benefit issue is usually discussed on a case-by-case basis", states Dr. Frauke Naumann-Winter. Application for orphan designation is often submitted at a very early stage when no clinical data are available at all. In these cases we must examine whether the pharmacological approach is plausible and whether the assumption of a major benefit over established methods can be scientifically documented. Then, at the time of authorisation the assumptions must be supported by clinical data.

Future challenges need to be faced and regulations adapted to current developments. In November 2015 the European Commission published a "Notice from the Commission" for comments (deadline 15 February 2016), in which "major benefits" are to be defined more clearly.

*"The major benefit issue is usually discussed on a case-by-case basis"*
***Dr. Frauke Naumann-Winter, Member of the Committee for Orphan Medicinal Products***

# Safety: Responsibility of Parallel Importers is Growing

Measures to reduce risks from medicinal products are to be implemented by parallel importers and authorisation holders for reference products alike.

Within the European Union (EU) and the European Economic Area (EEA), Germany is the country with the highest rate of medicinal products coming through parallel import. In recent years applications for new parallel import authorisation received by the BfArM per year have levelled out at about 500. Also parallel importers from other European Member States regularly apply for and receive parallel import marketing authorisation by the BfArM.

Parallel importing is a business model that has emerged from the diverging price levels for medicinal products in the Member States. Pharmaceutical companies place large numbers of medicinal products on the market both in Germany and in other Member States of the EU and/or the EEA. For each medicinal product companies have a separate national marketing authorisation in each Member State where their product is placed on the market. Parallel imported medicines are those products that are purchased in one of the Member States by firms that are independent of the original authorisation holders or manufacturers. The purchased products are then imported into Germany and placed on the market in parallel to the medicinal products already authorised in Germany.

In Germany only pharmaceutical companies are entitled to the marketing of medicinal products. Hence, in the regulatory meaning parallel importers are pharmaceutical companies with all the resulting rights and duties. So they must appoint a risk management representative as well as an information representative. Parallel importers need a manufacturing license for the repackaging of parallel import products because the containers and outer packaging must be provided with German language labelling and German language package information leaflets. Like pharmaceutical companies parallel importers are subject to monitoring by the competent health authorities of the laender (Landesbehörden).

Besides, parallel imported medicinal products must have national marketing authorisations of their own in Germany in order to be marketable here. However, instead of having to meet the usual requirements they undergo a simplified marketing authorisation procedure where only certain documents are required for submission.

Since parallel importers do not hold the marketing authorisation dossiers containing proof of quality, efficacy and safety for the medicinal products to be imported, the parallel imported products must be sufficiently similar to the products that have already received valid marketing authorisation in

Within the European Union and the European Economic Area, Germany is the country with the highest rate of medicinal products coming through parallel import.

Germany, the so-called reference medicinal products. For the products to be imported parallel importers may refer to the documents proving efficacy and safety of the reference products. This approach is possible because requirements for proof of quality, efficacy and safety have been harmonised in all EU Member States.

The responsibility of parallel importers has grown in recent years, first of all with regard to the safety of medicinal products and protection from falsification, in so far as parallel importers are obliged to guarantee patient safety in the same way as any other pharmaceutical company.

In 2011 the EU Directive on Falsified Medicines came into force. Its implementation entails changes also for parallel imports, such as serialisation by a two-dimensional bar code and anti-tampering device on the outer packaging of each product. These safety features are to be re-attached to the imported products after their repackaging.

The changes in the European pharmaceutical legislation and the national implementation in the Medicinal Products Act (AMG) imply further obligations in the interest of safety for patients and of medicinal products. For instance, being pharmaceutical companies, parallel importers must have available a pharmacovigilance system laid down in writing in a Pharmacovigilance System Master File. Like in Good Pharmacovigilance Practice the File is subject to inspection at the parallel importers' sites by inspectors of the higher federal authorities (BfArM or Paul-Ehrlich-Institut). In case of deficits parallel importers are required to present measures to remove them.
For products under additional monitoring, parallel importers are obliged to have a black inverted triangle displayed in the labelling of the German package leaflet and summary of product characteristics of the repackaged parallel import product. Additional monitoring is required, for instance, for novel active substances for which only limited data on certain risks are available at the time.

The BfArM would like to stress that further measures of risk reduction are implemented by parallel importers in the same way as by the authorisa-

The implementation of the EU Directive on Falsified Medicines of 2011 has entailed changes also for parallel imports, such as serialisation by a two-dimensional bar code and anti-tampering device on the outer packaging.

tion holders for the reference products. Such measures include, above all, instruction material and controlled dispensing systems as may be ruled for reference medicinal products in order to further reduce drug-related risks. Patient safety is BfArM's highest priority. No discrepancies in the safety assessment should be tolerated between reference products and parallel imported products. The BfArM will actively campaign for this aim both on the national and the European level.

# BfArM: Companies Should Report Supply Shortages

Data shall help to identify potential supply gaps as early as possible and to support companies in problem solving.

The proper supply to humans and animals of medicinal products of a proven quality, efficacy and safety is the very purpose of our pharmaceutical legislation (Section 1 of the Medicinal Products Act/AMG). Although over 100,000 medicinal products are marketable in Germany, there is an increasing number of cases where the proper supply of medicinal products is not guaranteed because authorised products are not available at all or not in the necessary quantity. Included are even medicinal products for the treatment of life-threatening or serious diseases for which no alternative preparations are available.

“Some companies seem to have no plan B for the manufacture of their medicines“, says Dr. Michael Horn, Head of Licensing Division 1. “There is no other explanation why for many medicinal products active substance production relies on only one manufacturer. This may be more economical for a company but it is certainly not in the interest of patients.“

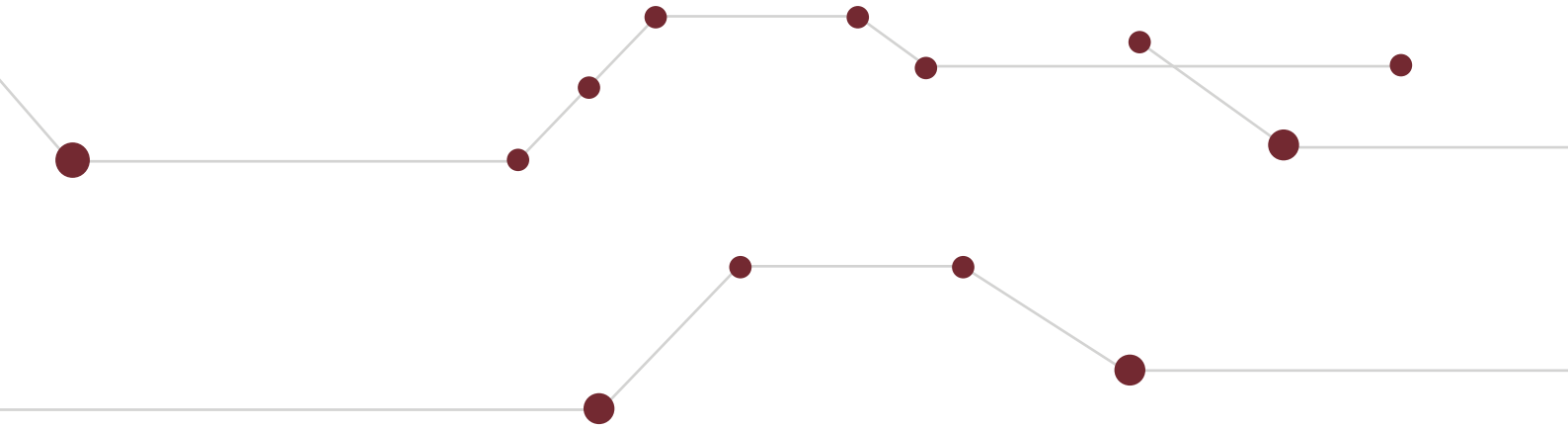
In fact, in about 70 per cent of the supply shortages reported to the BfArM the reasons mentioned were manufacturing problems and in about 25 per

cent insufficient manufacturing capacities. All in all there is a variety of reasons for supply shortages (see Table 1). Manufacturing problems may emerge, for instance, because a manufacturing process is under conversion or manufacturing capacities must be increased thanks to increasing demands. Yet, a growing number of shortages is due to inadequate quality. As a result of industrial concentration processes an ever decreasing number of manufacturers take over the production of active substances. If a manufacturing site drops out then all of a sudden the active substance is no more available for any of the authorisation holders.

*"We soon need a comprehensive picture of supply shortages, especially of relevant medicinal products".*
***Dr. Michael Horn,***
***Head of Licensing Division 1***

*Table 1 Reasons for supply shortages*

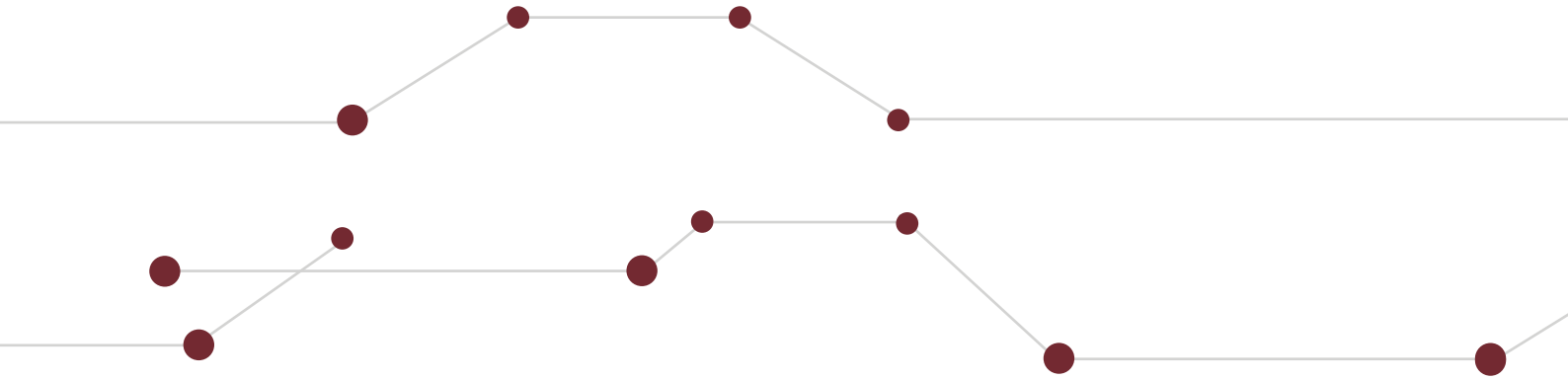
| Capacity planning | Manufacture | Distribution |
|---|---|---|
| · Wrong demand estimates<br>· Inadequate manufacturing capacity<br>· Reduced storage capacity | · Non-availability of active substance, mainly due to Good Manufacturing Practice status of manufacturer<br>· Batch-related manufacturing problems<br>· Complex time-consuming manufacture | · Problems in supply of active substance and excipients<br>· Problems with wholesalers, e. g. because of Good Distribution Practice status<br>· Revocation due to suspicion of counterfeit |



For this reason a voluntary reporting scheme was introduced for all authorisation holders in early 2013 and a register of reported supply shortages was published on the BfArM website. “The purpose of the shortage register is the better information of the public about an acute shortage of medicinal products for the treatment of life-threatening or serious diseases. This can only be a first step“, states Dr. Michael Horn. “We soon need a comprehensive picture of supply shortages, especially of relevant medicinal products“.

It is desirable that companies commit themselves to reporting supply shortages to the BfArM. This would enable the BfArM to identify potential supply gaps earlier and help resolve the problems with its expertise and knowledge of the available data. The BfArM is already concerned with checking whether and, if so, how many alternative preparations would be available in cases of manufacturing problems. On the basis of a long list of indispensable medicinal products a risk-adapted list has been drawn up, which has been agreed with the expert associations and which is permanently reviewed and continued. According to Dr. Horn it is already an important reference in the differentiated handling of supply shortages. It may be considered under the terms of Section 52b AMG to require expanded stockpiling of those medicinal products that are included in the list of active substances.

For the better evaluation of reported supply shortages in the future, the BfArM intends to include sales volumes and data related to prescription volumes in the assessment of medicinal products. For a structured transmission of the related data to the BfArM a submission portal will be designed in the near future.



A list of the current supply shortages for human medicinal products in Germany is presented on www.bfarm.de/lieferengpaesse, on the basis of the information voluntarily provided by authorisation holders.

The table contains medicinal products within the competence of the BfArM and the PEI (Paul-Ehrlich-Institut). Information relating to supply shortages of vaccines for human use against infectious diseases is found on www.pei.de/lieferengpaesse-impfstoffe-human

## Background: Not every supply shortage is relevant

According to the BfArM the supply of a medicinal product is relevant if the following items apply cumulatively:

- The disease to be treated is life-threatening or irreversibly progressive or does severe harm to the patient, if not treated. This applies to acute situations (emergency), chronic situations or potentially fatal situations, in which the medicinal product has a positive impact on the course of the disease (EMA criteria).
- The medicinal product is relevant to the entire population.
- No therapeutic alternatives are available.
- Risk of supply shortage is relevantly increased.

An increased supply risk is assumed especially if there exists only one manufacturer of the active substance or of the finished product, or if the medicinal product is placed on the market by only one pharmaceutical company.

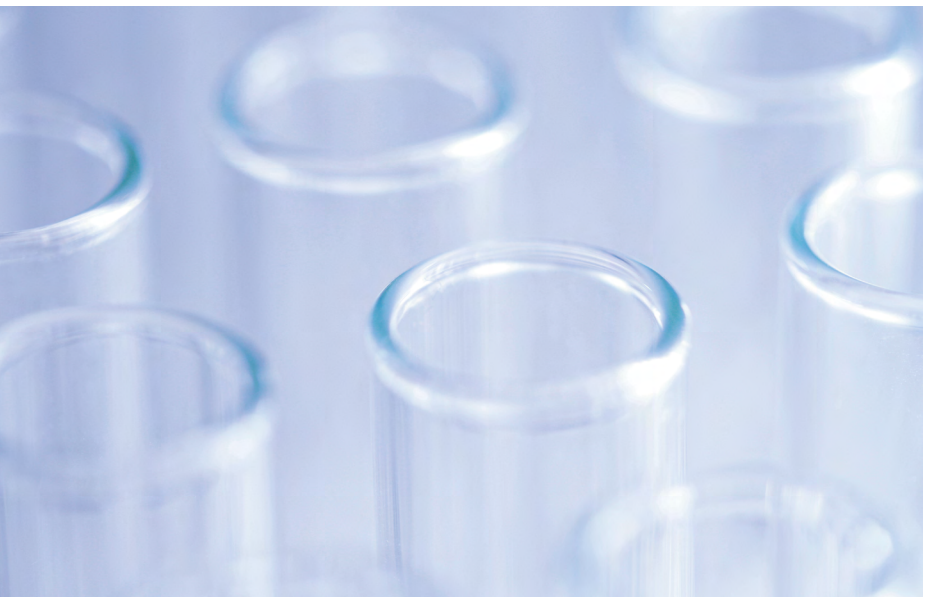
Since 2013 the BfArM has received a total of 100 reports of supply shortages with 60 cases resolved in the meantime. The indication areas particularly affected by the supply shortages were anti-infectives for systemic application, anti-neoplastics, and immune modulators (see Table 2). The European legislation does not provide for a statutory duty of companies to place their authorised medicinal products on the market. In fact companies have the right to withhold their products from marketing for three consecutive years. Looking at deregistrations pursuant to Section 29 para 1c AMG, about 8,500 marketable medicinal products (equivalent to about 20 per cent of the medicinal products liable to notification) are currently not placed on the market, within the competence of the BfArM. However, once a medicinal product is placed on the market the pharmaceutical company is liable to ensure adequate and continuous supply of the product in Germany under Section 52b AMG.

*Table 2 Statistic evaluation according to ATC-code frequency*

| ATC-Code | Percentage |
|---|---|
| Anti-infectives for systemic use | 24% |
| Anti-neoplastics and immune modulators | 20% |
| Cardiovascular system | 11% |
| Nervous system | 11% |
| Systemic hormone preparations, excl. sex hormones and insulins | 8% |
| Anti-parasitic agents, insecticides repellent substances | 5% |
| Others | 21% |

# Clinical Trials: Future Authorisation via EU Portal

Ethics committees and competent authorities cooperate more closely in assessing applications for clinical trial authorisation.



Future authorisation procedures for clinical trials of medicinal products for human use, will be ruled by Regulation (EU) No. 536/2014, which replaces Directive 2001/20/EC as the previous legal basis. Although EU Regulations are immediately applicable law in all Member States, the present Regulation allows for certain national specifications, for instance, for clinical trial assessment by ethics committees. Under currently applicable law ethics committees and competent authorities review applications for authorisation completely independently of each other. For this reason sponsors must currently submit their applications both in writing and on electronic media separately to the competent authority and to all involved ethics committees. At present a clinical trial cannot be started until the responsible ethics committee and the competent authority have each given their approval. In future this two-track policy will be overturned by the above EU Regulation.

Applications will then be submitted exclusively electronically in a single package via an EU portal and each concerned Member State will issue its approval via this portal. In the new application for authorisation Part I contains all general aspects of the clinical trial, which are identical for all Member

States. Aspects of mainly national concerns, such as consent giving following patient information, data protection or recruitment procedures, are presented in Part II of the application. In multinational procedures Part I will be assessed by all concerned Member States under the aegis of the reporting Member State, while the aspects presented in Part II are exclusively assessed nationally in each Member State, and each compiles its own assessment report on Part II. The reporting Member State compiles the assessment report on Part I on behalf of all concerned Member States.

Whether and how a Member State will involve ethics committees in the granting of authorisation will be determined by the Member States themselves in their own national legislations. In Germany the coordination between ethics committees and competent authorities will be laid down in the impending revision of the Medicinal Products Act (AMG). The current draft proposal provides that the authorisation procedures will be administered by the respective competent authority. The content of Part II will be reviewed exclusively by the competent ethics committee, who will also compile the assessment report. While the content of Part I will principally be reviewed by the competent authority provided it is the reporting Member State. However, certain aspects of Part I will be commented by the ethics committee, and the competent authority will have to give due consideration to their comments

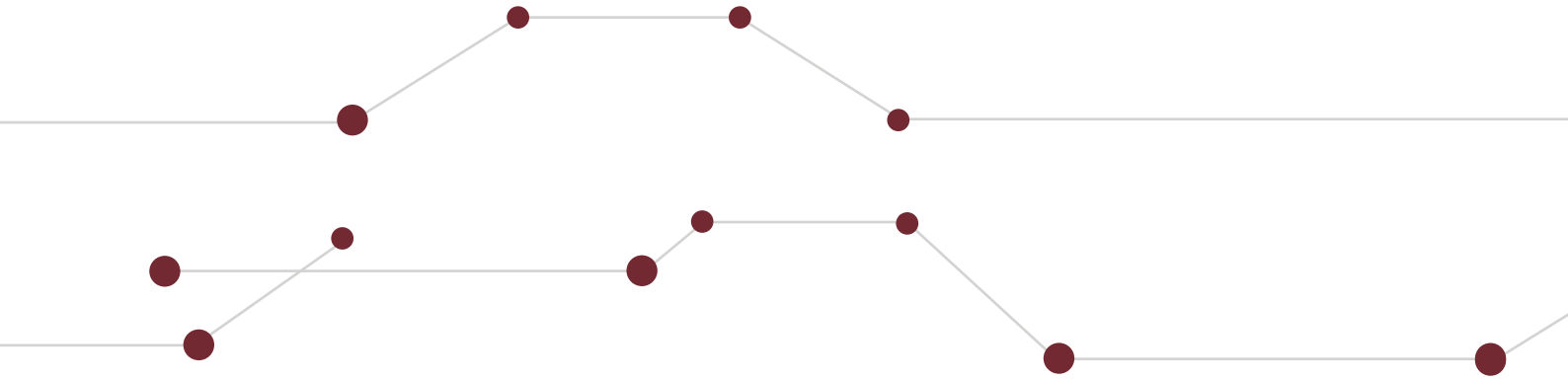
*"On the initiative of the BfArM a pilot project for joint application assessment has been installed. It is the aim of the project that we begin already now to jointly review the present applications for authorisation as far as possible according to the procedures and timelines as set out in the EU Regulation, but ensure at the same time that the granted authorisations comply with the currently valid provisions."*

***PD Dr. Thomas Sudhop,***
***Head of Scientific Services Division***

The Medicinal Products Act (AMG) will be amended as required by Regulation (EU) No. 536/2014 relating to clinical trials with medicinal products for human use. Through this Regulation the procedures for authorisation, conduction and surveillance of clinical trials become binding throughout Europe. The Medicinal Products Act regulates the national competences and procedures for the authorisation of clinical trials.

when drawing up or commenting the assessment report on Part I. The overall decision on the clinical trial will then be made by the competent authority on the basis of the assessment reports on Parts I and II of the application. Owing to the short timelines it is important that well-structured and transparent communication pathways are established between the competent authority and the ethics committees, especially for processing Part I of the application.

Although the EU Regulation will not be in force until 2017 at the earliest, the ethics committees as well as the competent authorities are already preparing for closer cooperation in the assessment of applications for authorisation. "On the initiative of the BfArM a pilot project for joint application assessment has been installed", says PD Dr. Thomas Sudhop, Head of Scientific Services Division. "It is the aim of the project that we start already now to jointly review the present applications for authorisation as far as possible according to the procedures and timelines as set out in the EU Regulation, but ensure at the same time that the granted authorisations comply with the currently valid provisions." Via a safe computer platform the competent ethics committee and the competent authority validate the application in a first step in



accordance with the timelines of the Regulation, thereafter they will jointly assess Part I on the basis of an assessment report. Excluded from the joint assessment are the pharmaceutical quality documents, which are evaluated by the competent authority alone, while the documents of Part II are evaluated by the ethics committee alone.

The pilot project gives the competent authorities, the ethics committees, and also the applicants the chance to get used to the new procedures, to match their processes to them and thus get prepared for the challenges of the new EU Regulation.

# Safer Distribution Channels, Protection of Patients

The theft of medicinal products in Italy revealed that tracking of falsifications is currently very difficult or limited. Expert advice from the BfArM is appreciated also in this connection.

Trade with falsified medicinal products has increased considerably in the recent years. The BfArM received 37 reports of falsifications in 2013 via the European rapid alert system, while the number had almost doubled to 60 in 2014 and kept this level with 64 in 2015. This development is a serious threat to patient safety. "We are aware of an increase in criminal structures, probably triggered by the high profit margin and the different price structures for medicinal products in Europe", says BfArM President Prof. Dr. Karl Broich. "Safety must be our highest priority here, because, after all, it is the most critically diseased persons who need protection."

In this context we should raise the question of safety for distribution channels and parallel imports. Thefts of medicinal products in Italy became known in 2014. Especially the German authorities were kept busy dealing with the ramifications. High-price medicinal products, among others anticancer agents, were affected. One parallel distributor in Germany noticed initially manipulated Herceptin, which had come from a theft in Italy. It turned out soon that it was not an isolated case, but that medicinal products had been repeatedly introduced illegally into the distribution chain in Italy, says Dr. Norbert Paeschke,

Head of BfArM Pharmacovigilance. In most cases the batch numbers printed on the vials and the expiry date were not identical with the corresponding labelling on the outer packaging. There were even cases where the active substance in the ampules was diluted and antibiotics were supplemented to prevent patients who received the products from catching infections, which would have uncovered the falsification too soon.

In the course of the investigations it was found that there were other important medicinal products that had been stolen in Italy, falsified and subsequently re-introduced into the legal distribution chain. Falsifications were found with various wholesale traders, parallel distributors, and importers both in Germany and in other European countries. Large-scale inspections of the suspected lots were necessary in Germany to identify the falsified medicinal products. The investigations had been instigated by the laender authorities (Landesbehörden), who are competent for the monitoring of manufacturers, wholesalers and pharmacies.

The higher federal authorities are responsible in such cases to inform the public timely and comprehensively. The BfArM plays a major role in the national and international exchange, it compiles all data concerning the investigations and interventions and coordinates the exchange with the other European regulatory agencies and the European Medicines Agency (EMA). In the case of the stolen medicines in Italy it was a particularly complex task, not least because it was imperative to prevent damage from critically diseased patients given the indications the falsified medicinal products were designed to treat. "The BfArM and the PEI (Paul-Ehrlich-Institut) provided detailed information to the professional circles, the media and the general public as soon as the first pieces of information came from the Italian health authority", underlines Dr. Paeschke. "Pharmacists and physicians were advised of the signs by which they could identify a possible manipulation. The higher federal authorities published the batch recalls and informed all stakeholders on the state of the investigations." Communication with the Italian authorities was handled by the higher federal authorities, while the measures of hazard control and its monitoring were the competency of the Landesbehörden. They checked the batches coming from Italy for authenticity and ordered the recall of the falsifications. 37 products

*"We are aware of an increase in criminal structures, probably triggered by the high profit margin and the different price structures for medicinal products in Europe. Safety must be our highest priority here, because, after all, it is the most critically diseased persons who need protection."*
***Prof. Dr. Karl Broich, President of the BfArM***

Patients who have a suspicion of product manipulation should contact the pharmacy where they have obtained the suspected product. Further information on how to recognise illegal medicines, especially under online sales conditions, is compiled at the BfArM website: www.bfarm.de/versandhandel

had to be recalled alone by the biggest of the affected German parallel importers. Apart from the BfArM, the PEI and the Landesbehörden, the operation involved quite a number of other institutions: the Federal Criminal Police Office (BKA), all State Offices of Criminal Investigation, the Customs Criminal Investigation Office (ZKA) and the Central Authority of the Länder for Health Protection with regard to Medicinal Products and Medical Devices (ZLG), as well as several prosecution and police stations. To ensure that the relevant information was communicated immediately to all recipients, the BfArM and the PEI established a joint working group of federal and laender authorities. So it was possible that the necessary measures were implemented timely and in close coordination.

Since this case has demonstrated how difficult the tracking of falsifications can be the BfArM is in constant touch with political bodies in order that safer distribution channels and better control of the supply chains get established, and last but not least, that falsification is made much more complicated, for instance by applying codes. These and further measures should be taken to make the complete retail and wholesale chain safer and easier to track. Expert advice from the BfArM is appreciated also in this connection.

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## Background: Falsification of medicinal products

**Falsified medicinal products** in the definition of the WHO are medicinal products that are deliberately and fraudulently mislabelled. This means that wrong information is given with regard to identity, active substances and/or source of product. This definition is also included in the European legislation and the Medicinal Products Act. Tracking and clearing-up of falsification is the competency of the monitoring authorities of the Bundesländer (laender) and the BKA (Criminal Police Office).

The BfArM received 37 reports of falsifications in 2013 via the European rapid alert system, while the number had almost doubled to 60 in 2014 and kept this level with 64 in 2015.

**Monitoring of the pharmaceutical market** is the competency of the Bundesländer (laender authorities); they monitor both the manufacture and the distribution of medicinal products including the stocks in hospital pharmacies. Monitoring of the pharmaceutical market in Europe is the competency of the competent authorities of the Member States. The European Medicines Agency (EMA) coordinates the activities including the information flow in cases of risks associated with medicinal products authorised in centralised procedures.

**Management of drug related risks** including falsifications, is centrally coordinated in Germany by the higher federal authorities (BfArM, PEI, Federal Office of Consumer Protection and Food Safety [BVL]) on the basis of the risk management plan (Graduated Plan Procedure pursuant to Section 63 Medicinal Products Act). Monitoring and the ruling of measures, however, is the responsibility of the laender. The collection of relevant information for the European agencies and the EMA is again the task of the higher federal authorities. The latter are also responsible for informing the public about falsifications and related interventions.

Consumers using **online purchase of medicinal products** should pay special attention to the legal status of the suppliers, i. e. check whether they are legal pharmacies authorised for on-line marketing. All EU Member States keep registers where the legal pharmaceutical suppliers settled in their respective territories are listed. In Germany the German Register of Online Medicine Retailers is kept at German Institute of Medical Documentation and Information (DIMDI). Pharmacies registered there may use a safety logo at their websites. A common logo for legally operating online pharmacies in the EU was introduced in June 2015. A click on the logo and you see the details of the pharmacy in the register.

For further information see: www.bfarm.de/versandhandel

# Faulty Studies: Strict Position of BfArM

When conduction of studies and data reliability in an Indian company were found to be severely faulty, BfArM was the first European agency to rule the suspension of authorisation for the affected generic products.


Severe faults in study conduction and in data reliability: This was the outcome revealed in the inspection in 2014 made by the French medicines authorities at GVK Biosciences in India. Data manipulation of electrocardiograms over a period of several years was found in most of the inspected studies. The BfArM was the first European agency to draw the conclusion from the incident ruling the suspension of authorisation for affected generic products in late 2014.

GVK Biosciences in Hyderabad (India) conducts the so-called bioequivalence (BE) studies for pharmaceutical companies. BE studies are necessary for generic products to receive authorisation in accordance with pharmaceutical legislation. The studies are to provide evidence that the generic product generates the same blood level of active substance as the original preparation. Contract research organisations (CRO) conducting such studies are randomly inspected by regulatory authorities. Data are controlled and the specifications as provided in the application documents are checked for validity. In such an inspection of the Indian CRO GVK Biosciences, the French medicines agency Agence nationale de sécurité du médicament (ANSM) et the produits de santé, revealed deficiencies in the studies which were the basis of authorisa-

tion for a number of medicinal products. Faulty electrocardiograms had been used in most of the inspected studies over several years.

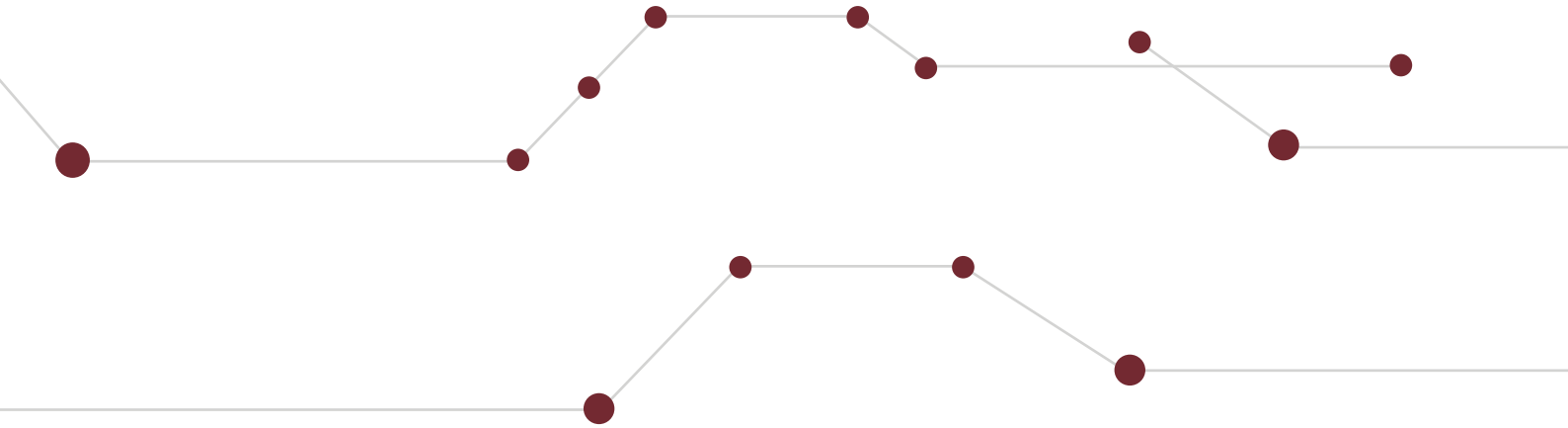
"For the purpose of prophylactic patient protection these bioequivalence studies were no longer acceptable as the basis of authorisation", states Prof. Dr. Karl Broich, BfArM President. "Therefore we decided at an early stage to rule the suspension of the national authorisations for the products based on the bioequivalence studies conducted by GVK Biosciences." This meant that these medicinal products were no longer marketable and were not allowed to be dispensed or sold by pharmaceutical companies, wholesale traders, pharmacies or other organisations.

In parallel to this national procedure, further marketing authorisations were reviewed for possible faults on the level of the European Medicines Agency (EMA). The BfArM was actively involved in the review. Dr. Harald Enzmann, Head of Licensing Division 2, represents Germany in the Committee for Medicinal Products for Human Use (CHMP) at EMA. When the faulty studies had become known, all generic product manufacturers were requested to present

*"We welcome that Europe has given a clear signal for compliance with our high ethical and medical standards in clinical trials."*
***Prof. Dr. Karl Broich, President of the BfArM***

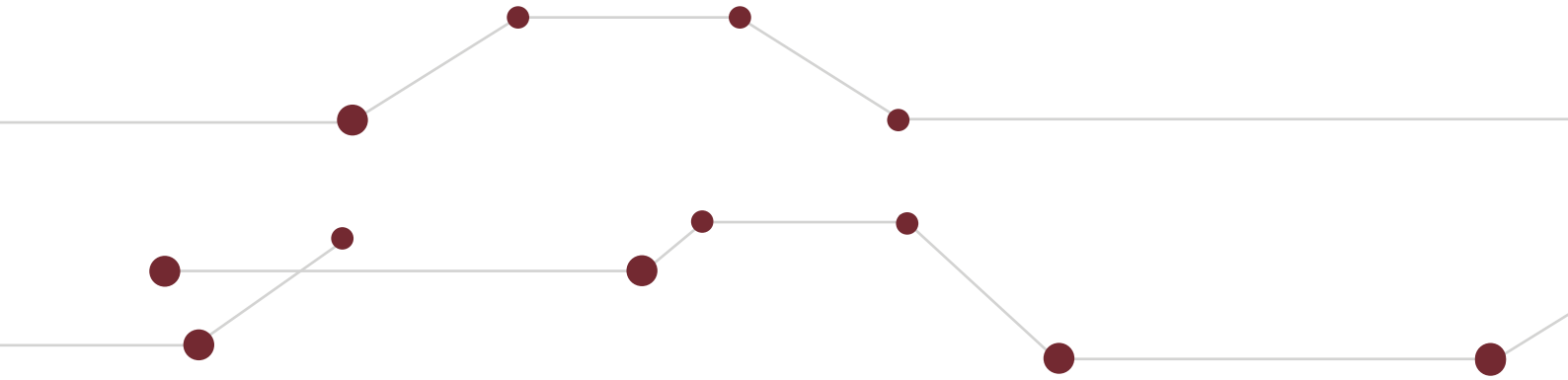
## Background: Bioequivalence Studies

Generic products, as any other medicines, may only be placed on the market if they have received authorisation. Authorisation requires submission of the proof that efficacy and safety of the generic product are similar to those in the original preparation (reference medicinal product), so that no new efficacy and safety studies are necessary. Similarity is demonstrated in a bioequivalence study proving that the active substance of the generic product achieves the same blood level as that of the reference product. Such studies are required for all products that are absorbed by the body before the active substance is released into the bloodstream. This is the case, for instance, for products that are metabolised in the stomach before the active substance gets into the bloodstream.



for review the studies conducted by GVK Biosciences. “In a process lasting for several months, more than 1000 authorisations from various Member States were reviewed“, reports Enzmann. “The CHMP issued the recommendation to suspend authorisation for about 700 pharmaceutical forms and strengths of the affected generic products.“ Even though there were no indications of an actual damage or direct risk for patients, it was the right decision for the purpose of maintaining the high European standards for the safety of medicinal products, underlines Enzmann.

BfArM President Broich appreciated the CHMP recommendation: “The critical position of the CHMP confirms our strict attitude towards prophylactic patient protection. We welcome that Europe has given a clear signal for compliance with our high ethical and medical standards in clinical trials.“ It is because of these standards that the BfArM is concerned about the decision of pharmaceutical companies to outsource more and more studies to threshold countries outside Europe. Severe deficiencies in trial centres remain the exception, yet “They show once again how important the inspections are and that the existing system of inspections functions well.“



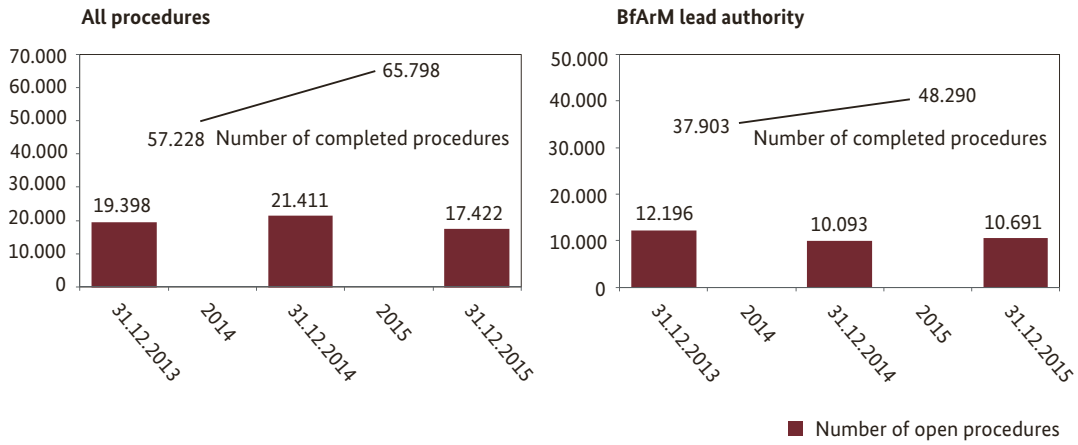
## Background: Inspections

The regular monitoring of contract research organisations (CRO) in third countries, as for instance GVK Biosciences, is principally the task of the country in whose territory the CRO is located. In the framework of authorisation procedure CROs are inspected by international teams. In the case of centralised authorisation procedures, EMA is in charge of the coordination of inspections, while coordination and conduct of inspections in decentralised procedures, and in mutual recognition procedures, which apply in the majority of generic products, is the responsibility of the Reference Member State, i. e. the Member State which is in overall control of the application assessment.

Rapp: Rapporteur · CoRapp: Co-Rapporteur · OMS: Other Member State · RMS: Reference Member State · CMS: Concerned Member State

* Figures include new licensing and registration applications as well as renewals and variations.

## COMPLETED AND OPEN LICENSING PROCEDURES 2014-2015




## TOTAL NUMBER OF LICENSING PROCEDURES

| | New applications* | | Completed procedures* | | Open procedures | |
|---|---|---|---|---|---|---|
| | 2014 | 2015 | 2014 | 2015 | 2014 | 2015 |
| National procedures | 28.192 | 40.301 | 29.518 | 38.929 | 6.761 | 8.181 |
| Decentralised procedures | 30.787 | 21.022 | 27.368 | 26.490 | 14.553 | 9.159 |
| Centralised procedures | 262 | 364 | 342 | 379 | 97 | 82 |
| **Total** | **59.241** | **61.687** | **57.228** | **65.798** | **21.411** | **17.422** |

## NATIONAL PROCEDURES

| | New applications* | | Completed procedures* | | Open procedures | |
|---|---|---|---|---|---|---|
| | 2014 | 2015 | 2014 | 2015 | 2014 | 2015 |
| Marketing authorisations | 250 | 268 | 243 | 262 | 341 | 347 |
| Registrations | 64 | 37 | 76 | 71 | 147 | 113 |
| Parallel imports | 492 | 484 | 490 | 388 | 309 | 405 |
| Variations | 26.690 | 38.743 | 27.570 | 37.789 | 4.632 | 5.634 |
| Renewals | 696 | 769 | 1.139 | 419 | 1.332 | 1.682 |
| **Total** | **28.192** | **40.301** | **29.518** | **38.929** | **6.761** | **8.181** |

## Medicinal Products

### DECENTRALISED PROCEDURES

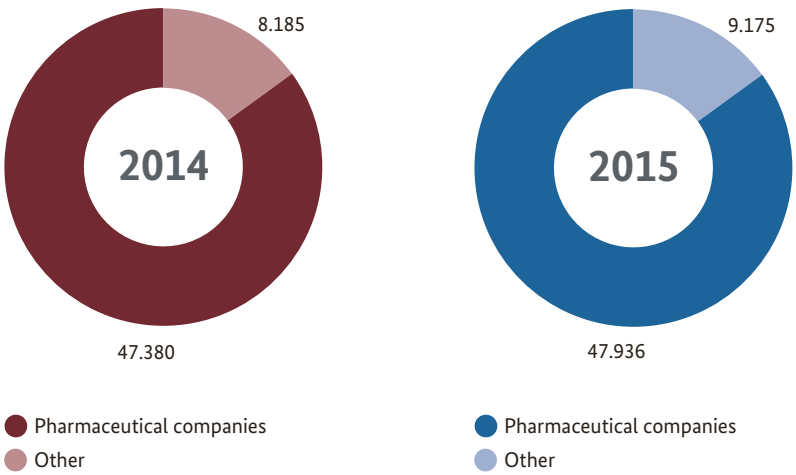
| | New applications* | | Completed procedures* | | Open procedures | |
|---|---|---|---|---|---|---|
| | 2014 | 2015 | 2014 | 2015 | 2014 | 2015 |
| Marketing authorisations | | | | | | |
| DC - DE = RMS | 738 | 553 | 476 | 570 | 867 | 850 |
| DC - DE = CMS | 655 | 728 | 621 | 611 | 1.003 | 1.120 |
| MR - DE = RMS | 6 | 4 | 11 | 3 | 14 | 15 |
| MR - DE = CMS | 69 | 111 | 61 | 90 | 63 | 84 |
| Variations | | | | | | |
| IA - DE = RMS | 2.750 | 4.768 | 3.401 | 5.088 | 598 | 278 |
| IB - DE = RMS | 3.046 | 2.151 | 3.077 | 2.551 | 708 | 308 |
| II - DE = RMS | 518 | 442 | 591 | 471 | 347 | 318 |
| IA - DE = CMS | 12.453 | 6.169 | 9.677 | 9.573 | 4.772 | 1.442 |
| IB - DE = CMS | 7.700 | 4.265 | 6.221 | 5.791 | 3.485 | 1.959 |
| II - DE = CMS | 1.817 | 970 | 2.237 | 843 | 742 | 869 |
| Renewals | | | | | | |
| DC - DE = RMS | 343 | 285 | 372 | 283 | 584 | 586 |
| DC - DE = CMS | 531 | 459 | 276 | 412 | 916 | 963 |
| MR - DE = RMS | 28 | 41 | 190 | 96 | 202 | 147 |
| MR - DE = CMS | 133 | 76 | 157 | 108 | 252 | 220 |
| **Total** | **30.787** | **21.022** | **27.368** | **26.490** | **14.553** | **9.159** |

### CENTRALISED PROCEDURES

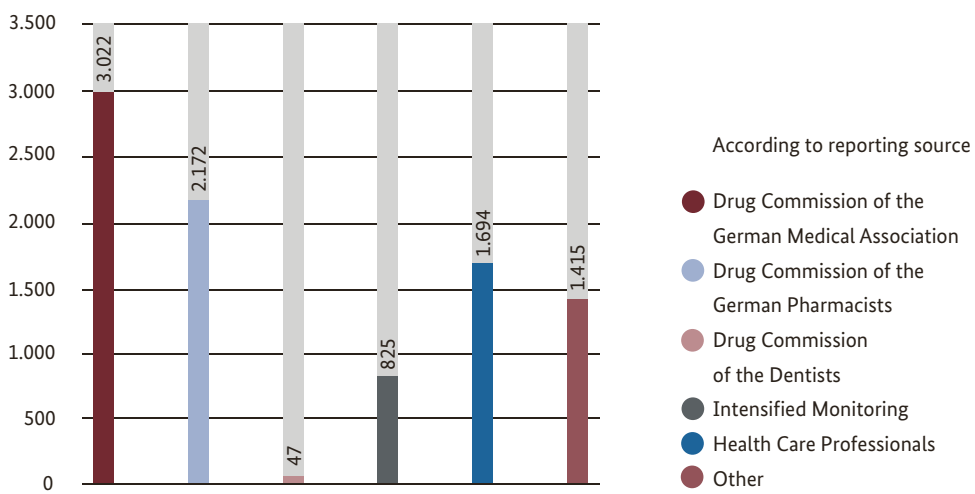
| | New applications* | | Completed procedures* | | Open procedures | |
|---|---|---|---|---|---|---|
| Marketing authorisations | 2014 | 2015 | 2014 | 2015 | 2014 | 2015 |
| DE = Rapp | 2 | 2 | 6 | 0 | 2 | 4 |
| DE = CoRapp | 7 | 4 | 8 | 5 | 5 | 4 |
| DE = OMS | 76 | 65 | 67 | 75 | 80 | 70 |
| Variations | 146 | 154 | 138 | 161 | 10 | 3 |
| Renewals | 31 | 139 | 123 | 138 | 0 | 1 |
| **Total** | **262** | **364** | **342** | **379** | **97** | **82** |

## NUMBER OF SUSPECTED CASES OF ADVERSE REACTIONS FROM GERMANY

According to reporting source



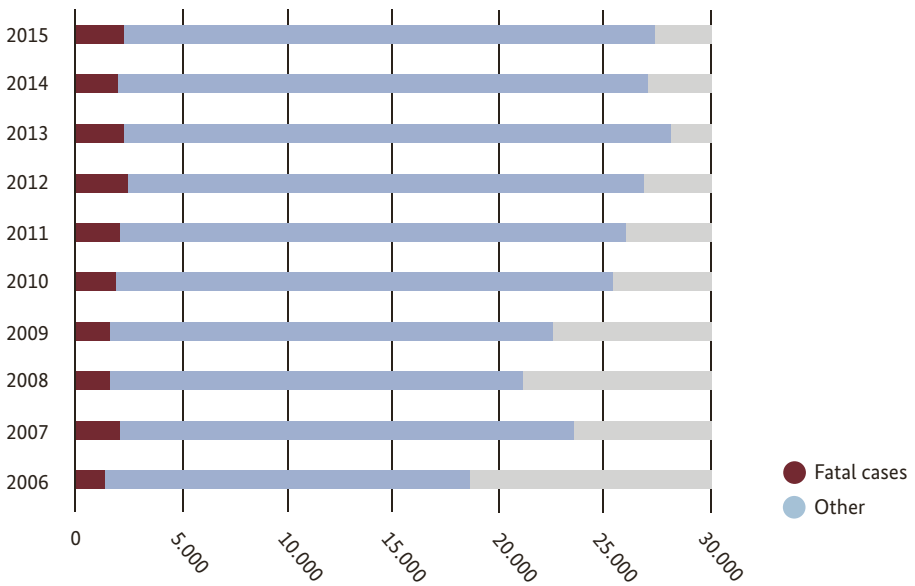

## NUMBER OF SUSPECTED CASES OF ADVERSE REACTIONS FROM GERMANY



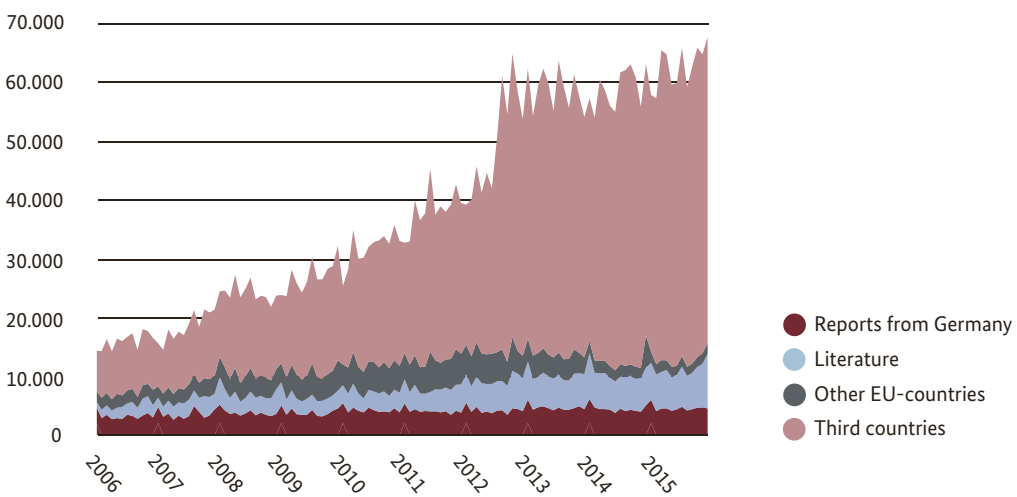

2015 (except pharmaceutical companies)

## Medicinal Products

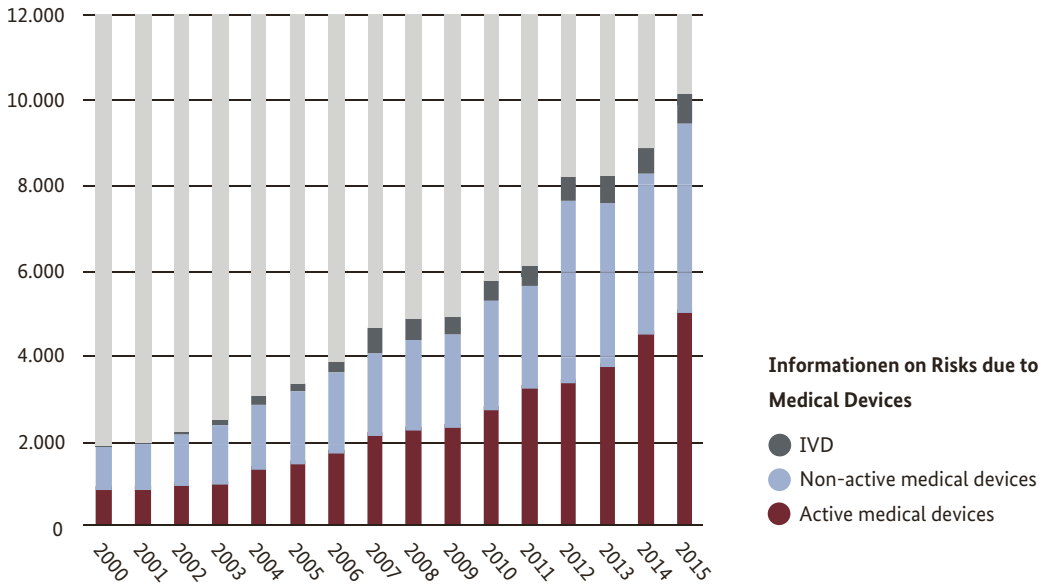
### NUMBER OF SUSPECTED CASES OF ADVERSE REACTIONS (DOMESTIC MARKET, NET)




### NUMBER OF SUSPECTED CASES OF ADVERSE REACTIONS PER MONTH



## NUMBER OF RISK REPORTS RECEIVED



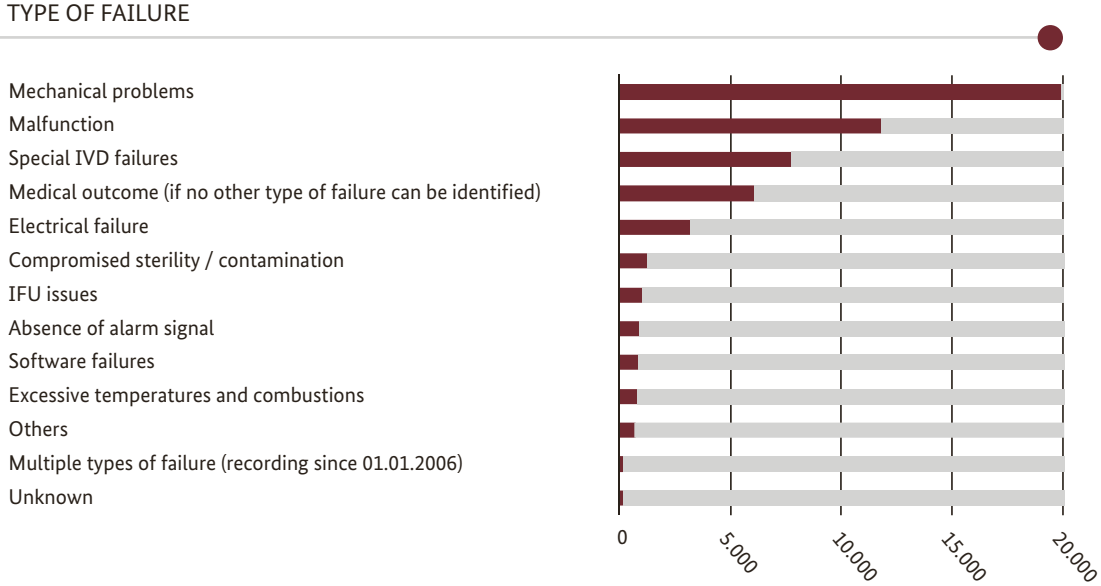

## DISTRIBUTION BY RISK CLASS

| | |
|---|---|
| Unknown | 4.838 |
| IVD General | 2.516 |
| Special Devices | 8 |
| IVD Devices for Self-Testing | 326 |
| IVD Annex II List B | 1.575 |
| IVD Annex II List A | 5 |
| Actives Implants | 12.122 |
| MD Class III | 7.775 |
| MD Class IIb | 14.001 |
| MD Class IIa | 6.307 |
| MD Class I with measuring function | 8 |
| MD Class I sterile | 150 |
| MD Class I | 4.116 |
| **Total** | **53.747** |

Statistical analysis of reports evaluated between 1 January 2005 and 31 December 2015

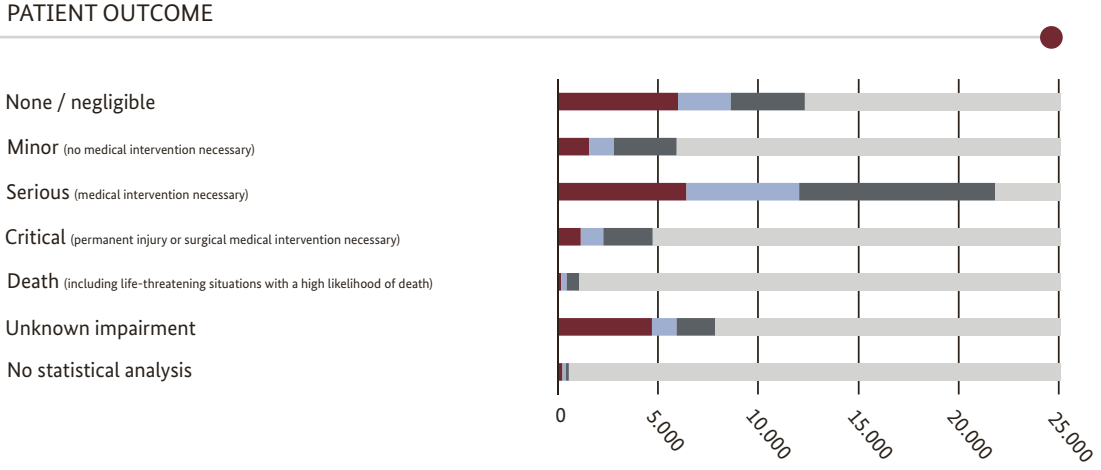
## Medical Devices

### TYPE OF FAILURE




Statistical analysis of reports evaluated between 1 January 2005 an 31 December 2015
Number of evaluated risk reports: 53.747, Multiple quotations possible (532)

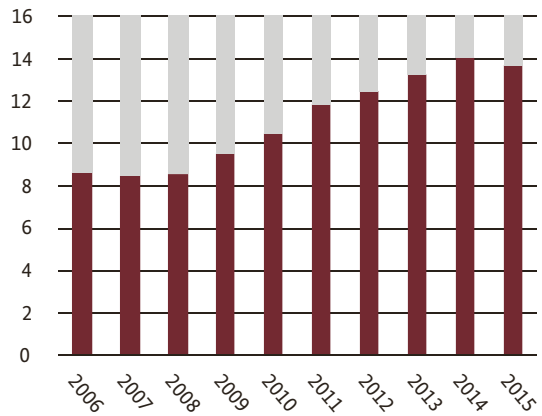
### PATIENT OUTCOME




- Device-related root cause
- Root cause unknown or not determinable
- Non-device related root cause

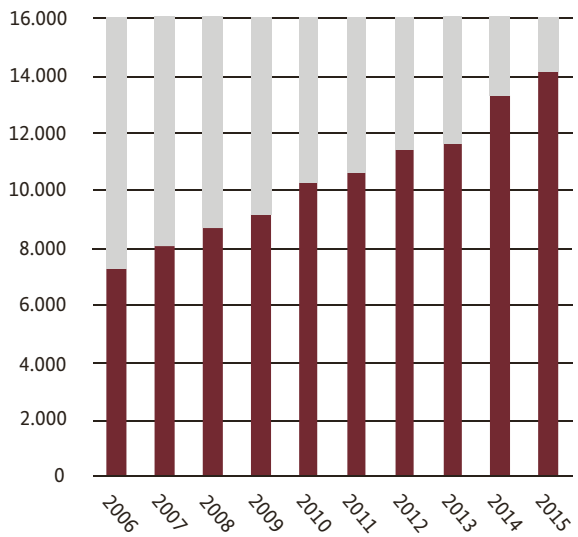
Statistical analysis of reports between 1 January 2005 and 31 December 2015
Number of evaluated risk reports: 53.747, Multiple quotations possible (532)

## DISPENSED NARCOTIC DRUG PRESCRIPTIONS - IN MILLION




Narcotic drugs, e.g. strong analgesics, medications for the treatment of opioid dependence or medicinal products for the treatment of ADHD, must be prescribed using a narcotics prescription form. These narcotics prescription forms are issued by the Federal Opium Agency to the prescribing doctors. In recent years, improved care of pain patients has led to a significant increase in the required number of narcotics prescription forms.

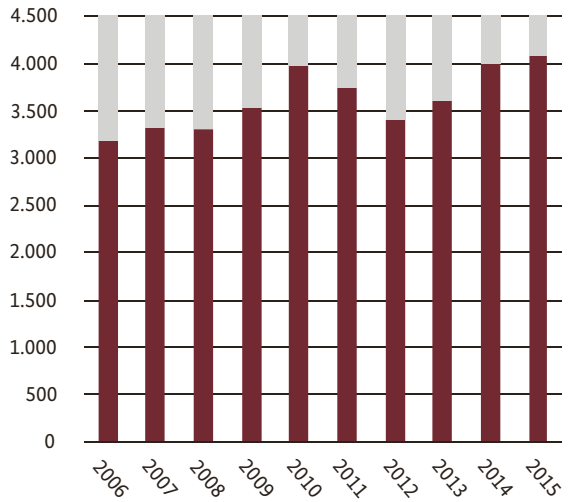
## IMPORT AND EXPORT PERMITS FOR NARCOTIC DRUGS




The cross-border trade in narcotic drugs is subject to special monitoring. In addition to the necessary licence, the importer and exporter require permits from the importing or exporting country before cross-border trade may take place. In Germany, these import and export permits are issued by the Federal Opium Agency.

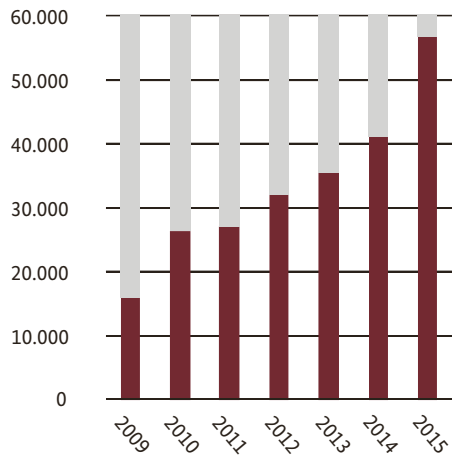
## Federal Opium Agency

### IMPORT AND EXPORT PERMITS FOR PRECURSORS




The cross-border trade in precursors is subject to special monitoring. In addition to the necessary licence, the importer and exporter require permits from the importing or exporting country before cross-border trade may take place. In Germany, these import and export permits are issued by the Federal Opium Agency.

### COPIES OF T-PRESCRIPTIONS EVALUATED




More than 50 years ago, the active substance thalidomide was responsible for the Contergan disaster. Since 2009, thalidomide and related substances are now once again being used therapeutically, subject to special monitoring. To prevent deformities in children, patients must receive extensive information before use. These active substances may only be prescribed using a special form, the “T-prescription”. The copies of these prescriptions are evaluated at the Federal Opium Agency in order to detect any incorrect behaviour by doctors or pharmacists at an early stage.