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DEAR READER,

The work of the Federal Institute for Drugs and Medical Devices (BfArM) has continued to be shaped by the processes of change over the last two years. Brexit is still a prominent topic. Through the withdrawal of the British authority, we will once more intensify our above-average commitment to European procedures. And we will also make a significant contribution to guaranteeing business continuity for the European Medicines Agency (EMA). There must be no delayed approval procedures or postponed risk assessment processes, for reasons of patient protection. Nevertheless, we firmly believe that this radical change will further strengthen the cooperative work between the EMA and the remaining national regulatory authorities.

Our new areas of operations, the Innovation Office and the Cannabis Agency, also demonstrate that we view ourselves equally as a partner for patients, professional circles, the industry and science and are proactively orientating our work to tackle new demands. Challenges for us as an

authority are also arising in staff recruitment, in the competition for the brightest minds. One more reason for us to place the focus of this annual report on our employees. As outstanding experts in international approval and risk assessment procedures, in medical device vigilance and in many other areas, they all dedicate passion and the necessary judgement to ensuring safe and effective treatment options. This also demonstrates the fact that working at the BfArM offers dedicated specialists interesting and varied opportunities to actively shape health in Europe – a highly attractive working environment, perhaps for you, too?

Finally, the images in this annual report on the topic of “Working at the BfArM” also take up a motif which was provided by the architectural art in our institute building in Bonn. The central message of the sculpture with its bright letters is “Don’t give up when you’re halfway there”. We view our dedication to safe healthcare in Europe with this in mind.



A handwritten signature in black ink, appearing to read 'K. Broich'.

Prof. Dr Karl Broich  
President of the BfArM



A handwritten signature in black ink, appearing to read 'J. Stingl'.

Prof. Dr Julia Stingl  
Vice President of the BfArM

## DON'T GIVE UP WHEN YOU'RE HALFWAY THERE

As the background for the photographs showing our staff members in this annual report, we very deliberately chose the “Der Schlüssel zum Code” sculpture situated in the entrance hall of the Federal Institute for Drugs and Medical Devices, the title of which means “the key to the code” in English. With this sculpture, the Swedish artist Jan Svenungsson has created a visual statement of the scientific merit of the institute within the scope of a public art competition. The sculpture contains a coded message and its solution. The work of art consists of the main sculpture in the entrance hall of the building, as well as six further satellite sculptures, which are positioned outside the building. The main sculpture bears three three-dimensional stacks of letters of varying heights made of polyester and painted in the colours white, pink, ice-blue and orange, which hide the key to the code. On the highest stack of letters, you can read the sentence “NICHT AUF HALBEM WEGE STEHEN BLEIBEN” (Don’t give up when you’re halfway there), the two other stacks repeat this plain text in code: YFAJEXSHSXJDPJUGRBQVPECPMICKMBL. By linking the plain text to the code, it is possible to decipher the encoded satellite sculptures made either of patina-coated bronze or different types of granite. The sculpture formations TACG, DVQVPJ, KRDCWI, RISGNH and XRR spell out IDEE, SYSTEM, ZUFALL, GLUECK and MUT (idea, system, coincidence, luck and courage), while the carpet of letters belonging to the main sculpture forms the word FORTSCHRITT (progress). Thus, the work of art symbolises scientific work as a form of deciphering, of searching for the key to the code. And with its key message, “Don’t give up when you’re halfway there”, the sculpture simultaneously epitomises the BfArM’s objective in driving forward progress in patient safety.



# Reliable patient care is paramount

Prof. Dr Karl Broich discusses the improved utilisation of potential innovations in pharmaceutical supply to patients, the activities and requirements of the Federal Institute for Drugs and Medical Devices (BfArM) with regards to big data, and the BfArM as an attractive employer with many creative opportunities.

## Patients are awaiting new, highly reliable treatment options. How can the BfArM help to shape the future of pharmaceutical supply in Europe?

Our involvement in European authorisation and pharmacovigilance procedures is aimed at sustainably improving patient supply and safety. In particular, we want to achieve optimisation in areas where there have, up until now, been either too few treatment options or none at all for specific applications or groups of patients. With approaches such as adaptive pathways, initially small and very specific groups of patients are able to benefit from new therapies on the basis of reliable scientific data. When at a later point additional data shows a positive effect for other, larger groups of patients, these too can benefit. This allows us to use potential innovations in patient care which would often previously have been lost. Again and again we see that companies draft their studies incorrectly. This not only means that potentially effective medications are lost, but also that patients may be treated with active ingredients which are not sufficiently effective for them due to their type of illness or genetic makeup. Hence, we are not only able to protect patients, but also generate proof

of efficacy for a well-defined group of patients. Here too, we need not only intensive communication with the industry, but also with patient representatives, who have the necessary expertise on the relevant disease or disorder. Another example is the patient group of children and young people, whose pharmaceutical situation

urgently needs further improvement. Here, we are in consultation with the parties involved and are thereby increasing the number of authorisations granted for patent-free medicines for children. Simultaneously, we are actively approaching paediatricians and parents in order to systematically overcome reservations about children participating in clinical studies.

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So that innovations reach the patients too, we help start-ups to close information gaps and set the right course through our Innovation Office.

PROF. DR KARL BROICH

**Brexit and the accompanying loss of the British authorities present a particular challenge for the remaining European authorisation authorities. What expectations are there for the BfArM and how is the BfArM positioning itself?**

Today, the BfArM is one of the major licensing authorities in the EU. We actively support the European Medicines Agency (EMA) in all key areas of drug authorisation and drug safety. Together with the Paul Ehrlich Institute (PEI), more than of our 480 experts bring their expertise



to around 130 scientific bodies of the EMA. We thereby already make significant contributions to the supply of patients in Europe with safe and effective medications – and will increase these contributions in the years to come, since after Brexit and the accompanying loss of the British licensing authority, the number of authorisation processes will also increase for Germany in particular. There is therefore already more intensive cooperation between the EMA and the BfArM, but also among other European authorisation authorities. In addition, the relocation of the EMA will have substantial effects on its ability to work, particularly during the relocation phase itself. It is not impossible that important experts will leave the EMA. In the interest of European patients, this development cannot be allowed to result in later availability of new drugs or less active address of risks of already-approved drugs. In this situation too, safe treatment for patients must be paramount. The EMA is therefore very significantly dependent on close cooperation and intensive communications with large national authorisation authorities, as has been the case up until now between the EMA and the British licensing authority.

**With the Innovation Office, the BfArM is responding to the need for information and advice for start-ups and research institutions. Does this show the contemporary services authorities need to offer to their stakeholder groups in the future?**

Start-ups and research institutions are indispensable driving forces for innovative therapeutic options, for example in the fields of dementia drugs, antibiotics or medical apps. If we want to continue to guarantee medical care for patients in the future, we need to use this enormous potential for innovation. However, in practice it is often the case that these small, young companies are often not particularly competent with regards to regulatory aspects. Many rules are simply not known to them. Subsequently, these companies frequently make the wrong decisions in the



early phases of development. Exciting innovations then often remain unused. With the Innovation Office, we therefore provide targeted regulatory support in the earliest stages of development. We help to close information gaps and set the companies on the right path for regulatory processes from the beginning. The goal behind this is to make sure that effective, safe innovations actually reach patients and do not fall at presumed hurdles in the areas of authorisation and certification before reaching the market. At a European level, we also bring this expertise in early consultation and in the inclusion of patients, specialist groups and HTA establishments in the form of the EU Innovation Network and the PRIME initiative. The positive response to this offer validates our active approach: as an active health authority, we directly approach our stakeholder groups and offer them a needs-oriented dialogue. At the same time, we want to promote translational research in university medicine and reinforce its use for prevention, diagnosis and treatment in research, teaching and further

education by expanding our collaborative work with universities and research institutes.

**On the subject of new treatment options: Where do you see the advantages of biosimilars and what contributions can the BfArM make in this area?**

Biosimilars offer enormous opportunities when it comes to improving patient access to high-quality yet affordable medications. These generic biopharmaceutical products have thus far been proven to be just as effective and safe as the relevant original product. Nevertheless, there are problems with acceptance from doctors, patients and the pharmaceutical industry. We therefore aim to help with increasing the number of authorisations for biosimilars by initiating a more intensive dialogue on the subject. The joint goal of all parties in this sector should be to better use existing potentials, in order to improve the availability of new treatment options. As a licensing authority, our focus is thereby above all the question of clear standards for safety and effectiveness.

**The BfArM has taken on completely new functions with the establishment of the Cannabis Agency. What is your intermediate conclusion?**

The new law is an important step for seriously ill patients who rely on treatment with medical cannabis. The Cannabis Agency means that we can help to ensure supplies of pharmaceutical-quality cannabis. To this end, we have broken new ground in many areas. Without being able to fall back on existing rules or experience, we have made long-term decisions aimed at safe patient care. Our first aim was to initiate a tender procedure for a total of 6.6 tonnes of cannabis. This was rightly perceived by the public as an excellent tender procedure and led to an enormous response from all sides. Although we had to make interim readjustments, we will eventually have developed a legally and professionally solid concept, with our experts' intensive preparations and dedicated efforts, and will subsequently reach a sustainable outcome. With a view to future supply, the accompanying study is of particular importance. The obtained data will form the basis of further clinical research, with the long-term aim of obtaining authorisation for finished medicinal products on the basis of cannabis.

**In the "conflict area" of health, authorities are increasingly confronted with expectations of ever faster and more transparent decision-making processes. How is the BfArM handling this challenge?**

Public interest in our work is rapidly increasing. This makes it understandable that public perceptions and depictions of actions on the part of authorities are also always influenced by high expectations when it comes to speed and transparency of decisions. But as shown by the example of the Cannabis Agency, among others: our decision-making and implementation processes are mostly directly linked to detailed scientific evaluations or complex administrative requirements. Both make careful investigation with a sense of proportion necessary. This applies to both possible safety procedures stemming from new studies and the implementation of court decisions. We must be able to credibly explain why we make the





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The BfArM offers enthusiastic experts an attractive workplace with the opportunity to actively participate in shaping health in Europe.

PROF. DR KARL BROICH

decisions and take the actions we do. This was outstandingly demonstrated by the decision of the Federal Administrative Court on the acquisition of a lethal dose of sodium pentobarbital. From our perspective, the enormous significance of the decision required careful analysis of the legal impacts and possible consequences, in order to do justice both to the judgement and to the individual situation of the patients. We are well aware of the fact that the affected patients and the public would have liked quicker information and decisions in the matter.

**With the tremendous developments in the field of big data, the BfArM must continually change and repeatedly re-establish itself in an up-to-date manner. How successfully can an authority do this?**

In the fields of pharmaceuticals and medical devices, we see great opportunities to soon be able to scan and evaluate large quantities of data more systematically and quicker by using new technologies in a more intelligent and customised way. For example, we are staying abreast of the rapid changes by establishing the new specialist area “Methods research and medical device safety”. With these activities, we are clearly leading the field on a European level. Further important developments, such as the new rules on clinical trials and the accompanying responsibilities, are already being intensively driven forward by both the EMA and the BfArM. Together with our experts, I myself, as the chair of the EU Telematics Management Board, am actively committed to enhancing drug authorisation and risk monitoring through innovative IT solutions, among other tools.

Our aim is to continue developing the BfArM towards an “Authority 4.0” model, with a view to the intelligent use of contemporary IT solutions.

**The expertise of the BfArM is directly linked to its employees’ competence and dedication. How does the BfArM position itself in the competition for the brightest minds?**

First, I can say that we are excellently positioned for upcoming challenges with our excellent employees. Whether it is the Cannabis Agency, the Innovation Office, increasingly complex authorisation procedures, closer pharmacovigilance or Brexit: we know that we will need to continue meeting the increasing demands made on us. We have made the necessary strategic personnel decisions and are constantly adjusting these in line with contemporary personnel recruitment. However, the topics of this annual report also show: the BfArM offers dedicated experts attractive jobs and many possibilities for actively helping to shape health in Europe. Where else, for example, do doctors have the opportunity to participate directly and effectively on a European level in questions relating to reliable patient care? At the same time, we offer attractive development opportunities, for example residencies. And the close connection between our regulatory work and our research activities and cooperative agreements, our intensive scientific junior development program and our numerous national and international scientific research cooperative agreements offer a wide spectrum of academic career possibilities, as was shown not least by our successful recruitment of a W2-level professor.

# Regulatory research: promoting young talent

The demand for trained scientists in the field of regulatory research will continue to increase in the future. The BfArM is already supporting trainee programmes with the aim of helping to meet this demand.

What challenges will the BfArM, as a researching higher federal authority, have to rise to in the future? What regulatory requirements will the scientists of the future need to address? The Federal Institute is already investigating these and similar questions. In the process, an important task is the promotion of young scientific talent in the field of regulatory research. The vice-president of the BfArM and leader of the research department, Prof. Dr Julia Stingl, supports targeted reinforcement of the qualification of young talent.

**Prof. Stingl, why is regulatory research so important for the work of the approval authorities and the drug development process?**

Modern medicine and the entire healthcare sector are constantly developing. These developments give rise to many new questions for authorities to deal with. This makes targeted and independent regulatory research important to close gaps in knowledge. The research helps authorities to perform their official tasks and delivers evidence for future regulatory measures. For this reason, internal research is part of the legal mandate of the relevant higher federal authorities. Regulatory research projects can thus address questions relating to the methodology of regulatory inspection or monitoring tasks. Or topics which affect the

safety and effectiveness of drugs or treatment methods in the population at large.

**What are the special challenges which need to be addressed by regulatory research in the future?**

We are already on the ball with internal research regarding special challenges such as the topic of “global health”, i.e. the question of how to handle cross-border health risks such as resistance to antibiotics. In addition, “big data”, the systematic analysis of large amount of health-related data, will become an increasingly important topic. This comes along with personalised medicine, whereby treatment concepts and drugs will be matched to the patients’ individual genetic make-up. The risk-benefit assessment for treatment methods will become increasingly individualised and will have to take account of genome data, as is currently forming part of cancer medicine in the form of next generation sequencing (NGS) technologies. We can also speak here of “Next Generation Regulation”. There are ongoing research projects in the BfArM on this topic as well.

**How do you aim to convince young scientific talent to work in regulatory research?**





PROF. DR JULIA STINGL

We need a wide range of opportunities, for example in the form of a type of postgraduate school which appeals to as many young scientists as possible and qualifies them for a career in the field of regulatory sciences. These kind of research programmes should be deliberately focused on “tomorrow’s regulatory requirements”. Ideally, PhD positions on these topics would be offered continuously, allowing fitting doctoral projects to be supervised directly in the institute itself. This allows us to achieve the optimal preparation for future regulatory tasks in health monitoring, regulation and prevention. A possible next step would be to further integrate the scientists into the institute’s work after graduation, for example as scientific assessors, so that they then profit from the experience gained by their own research in the field. The close networking between the sister authorities, the Robert Koch Institute (RKI), the Paul Ehrlich Institute (PEI) and the BfArM represents a particular advantage for the qualification programme, as the authorities pool competencies and expertise, offering the opportunity to organise joint projects.

**Internal regulatory research is already part of the BfArM’s legal mandate. What role will the promotion of young scientific talent in the area of regulatory research have to play here?**

Targeted promotion and qualification of young talent, for example in the form of doctoral programs, provides numerous benefits. In particular, the demand for independent regulatory-motivated research in the field of academic science is publicised, leading to an overall enrichment of evidence in academic clinical research. Through pre-research

projects, which usefully cross-institutionally connect the expertise of clinics, academic institutions and federal authorities, new regulatory questions which the authorities will need to handle in the future can be confronted more specifically and more extensively.

**What exactly do the research projects in question look like?**

We are already working on future-oriented projects, for example in the field of individualised medicine, where treatment methods and drugs will in the future be matched to the patients’ individual genetic make-up. Since 2017, the BfArM has been one of the project partners of the large European research alliance “HARMONY”, which consists of academic institutions and clinics, where we weigh in on regulatory questions. This project deals with the evaluation of large quantities of data from clinical research on treatments for leukaemia, in order to facilitate more exact prognoses and more efficient treatments for patients with leukaemia and other types of blood cancer in the future. In our “EMPAR” research project, which received 1.6 million euros of funding from an innovation fund, we are also currently researching the links between genetics and the effectiveness and safety of drug treatments. In particular, we are investigating whether genetic differences in drug substance metabolism have a discernible influence on the required dose and safety of drug treatments.

These examples show that future regulation will have a large demand for scientists trained to handle these questions, who are able to cover and further develop this area. In the interests of patient protection, the BfArM will continue to actively involve itself here and commit itself to appropriate support.

# Complex study designs: clinical trials for new therapeutic approaches

Through new therapy options, patients should benefit as much as possible from scientific progress. The study designs of clinical trials, which must be approved by the BfArM, are accordingly also becoming more complex.

Clinical trials are an essential prerequisite for the approval of new drugs. Furthermore, they provide patients and physicians with the opportunity to access not yet approved medicinal products, expanding the range of possible treatments available. “To ensure the safety of participants in clinical trials, the BfArM’s scientists examine every clinical trial during the application process. In doing so, they evaluate the documents on the pharmaceutical production of the drug under examination, the suitability and results of preliminary pharmacological and toxicological investigations and the test plan, which describes precisely how the study will be carried out,” outlines Dr Claudia Riedel on the core responsibility of the “Clinical Trials” specialist area, which she leads.

Through the approval process for clinical trials, the BfArM has the facility to influence the implementation of clinical trials in Germany. This equally benefits patient safety and research freedom. The BfArM queries around half of all initial applications and requests improvements or additional deliveries. In most cases, the BfArM’s requests are complied with, meaning that approximately 95% of clinical trials applied for are able to be approved. A further requirement for carrying out a drug trial on humans in Germany is approval from an ethics committee. The BfArM continues to monitor the clinical trials they have approved while they are running, to ensure that participants’ safety is not compromised by previously unidentified risks.

In recent years, scientific advances in molecular biology and immunology, which have for example contributed to a better understanding of tumour biology in cancer patients, have made it possible to develop new and more targeted types of therapy. This means that new treatment

options for different genotypable malignant tumours are available.

Increasingly, new types of therapy options require classical clinical trial design to be supplemented by new study concepts. The aim is to make the development process in the clinical trial phase more flexible and faster, in order to benefit patient care. In some fields, these advances have already led to more targeted treatment, particularly in oncology. Here, drugs are increasingly being developed which are specifically focused on the biology of the tumour, e.g. on growth factors or so-called driver mutations. Using certain biomarkers, patients can be divided into groups for different treatment schemes. On the one hand, this allows individually refined diagnosis and treatment for those patients who are most likely to respond to the therapy (individualised medicine). On the other hand, this sometimes also leads to significantly more complex designs for clinical trials: Modern testing concepts such as adaptive, umbrella or basket study designs often include a variety of different investigational drugs for the same underlying disease, or even a variety of different diseases. These will then be tested, partly parallel to each other and partly building on one another, using a single testing concept without the hitherto usual applications for further studies. “Applications for carrying out this type of clinical trial are thus becoming increasingly demanding. Furthermore, it should be noted that these complex testing processes must be evaluated by ethic committees and by the higher federal authorities BfArM and Paul Ehrlich Institute (PEI) working to very short deadlines,” emphasises Dr Riedel.

Adaptive study designs are characterised by the fact that aspects of the study design can be modified on the basis of



current study data. This can mean alterations to inclusion or exclusion criteria, the number of cases or the dosage of the test substance. Most modern study designs already include adaptive study elements. The aim of these adaptive studies is to quickly recognise and further develop promising therapy approaches – but also to stop less effective approaches in the early stages. Alongside these potential advantages of adaptive study designs however, there is a danger of distortion of the study results, i.e. vulnerability to bias and overestimation of effects, which can be difficult to verify.

In umbrella studies, various study arms are collected together as if under an umbrella. For example, an entity's tumours are generally scanned for various alterations on the basis of genomic or proteomic biomarkers. The patients are then divided into different sub-groups, who are treated with different active ingredients (different study arms). Umbrella studies often incorporate adaptive elements, such as flexible opening and closing of sub-studies or study arms, dependent on findings obtained during the study on the effects of the drug being investigated on a molecular target.

In basket studies, patients with different tumours are treated together in a common study protocol, because the different tumours show a common defined genetic alteration or expression of a target. For individual basket studies, however, the clinical value is questionable given the existence of further, hitherto unknown genomic alterations or different expressions of the therapeutic target. Additionally, with a view to clinical evaluation, cross-histology basket studies often cannot be monitored using a standard therapy arm, meaning that the results obtained can frequently only be compared in a limited way.

“These new study approaches are undoubtedly becoming more important and have a range of advantages. However, - due to the still high levels of uncertainty regarding the validity of the obtained results, patient safety and the practicability of carrying out the studies, from a regulatory point of view we currently see the acceptance of adaptive, basket and umbrella studies rather in an explorative, i.e. hypothesis-generating, setting. The results generated by these studies should then be confirmed by classical randomised controlled clinical trials.”

In 2017, this current development was also the trigger for the “Dialogue with the BfArM – Complex Study Designs” symposium in Bonn. During the conference, around 300 experts discussed the opportunities and challenges of increasing complex study designs. It provided the BfArM, the PEI and the Work Group of Medical Ethics Committees with a platform for dialogue with experts from universities, medical expert associations, pharmaceutical industry associations and ethics committees.

“Our goal is to promote dialogue between all parties involved and to achieve a better understanding, in particular for the fulfilment of regulatory requirements for complex study designs, and to jointly address new developments in the interests of patient safety,” says Dr Riedel.

The lectures of the  
“Complex Study Designs”  
event are available online at:  
[www.bfarm.de/komplexe-studiendesigns](http://www.bfarm.de/komplexe-studiendesigns)

# Global Health: joining forces in the battle against resistances

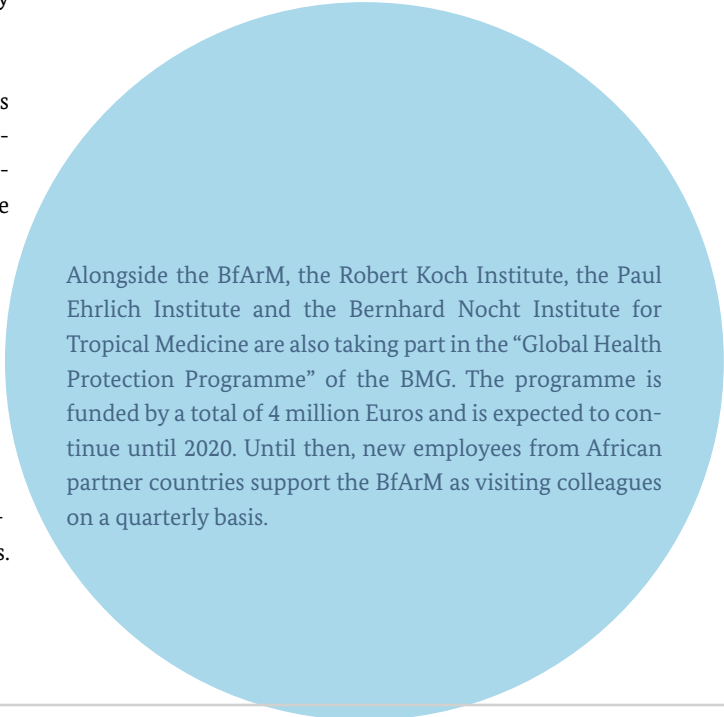
The BfArM is taking an active role in the implementation of the “Global Health Protection Programme” of the Federal Ministry of Health (BMG GHPP). By training qualified personnel in Bonn and implementing doctoral projects in Africa, the institute is making an important contribution to improving pharmaceutical supply.

In 2015, Germany and the other participants of the G7 summit committed to supporting the partner countries, for instance in the establishment of reliable health systems. Among other things, expertise on the assessment of the pharmaceutical grade of drugs will be passed on. Training courses on dealing with quality assurance and the accreditation of state laboratories for therapeutic drug monitoring will also be provided. The BfArM is participating in this programme and trains qualified personnel from African medicines authorities in the field of active ingredient analysis at regular intervals. In doing so, the institute cooperates closely with the World Health Organisation (WHO), together with whom the relevant training programmes were developed. Until the programme expires in 2020, qualified personnel from the partner countries, responsible for quality assurance in African laboratories, will be visiting the federal institute on a quarterly basis. This exchange is ultimately bound to be greatly beneficial to patient safety in Germany.

“The topic of drug therapy safety management must always also be viewed in a global context,” declares Project Coordinator Dr Nadina Stadler. “By improving the pharmaceutical grade of therapeutic drugs in African countries, we are at the same time improving the situation worldwide. A good example for this is the introduction of young scientists to the issue of the development of drug resistances in clinics, as the way in which the drugs are prescribed does not correspond to the principles of rational antibiotic therapy. As a consequence, fatal resistances then develop.”

For this reason, the exchange focuses on expertise in the assessment of the pharmaceutical grade of therapeutic drugs.

In many of the African partner countries, the situation must be seen critically. Among the most common safety hazards in these countries are for instance the false specification of the active ingredient content or an excessively high degree of contamination. “Such deficiencies may, in particular in the case of drugs for the treatment of infectious diseases like malaria, cause fatal resistances to develop,” says Dr Stadler. “For this reason, we concentrate primarily on the analysis of active ingredients.” In close cooperation with the colleagues at the WHO, a training programme has been developed which is designed to meet the requirements of the participating partners in eight African countries so far. The programme also gives the participants the chance to practice, using drug samples specifically from these countries. For example, the African scientists determine the pharmaceutical grade of the drugs with infrared spectroscopy. For this they are not only provided with the



Alongside the BfArM, the Robert Koch Institute, the Paul Ehrlich Institute and the Bernhard Nocht Institute for Tropical Medicine are also taking part in the “Global Health Protection Programme” of the BMG. The programme is funded by a total of 4 million Euros and is expected to continue until 2020. Until then, new employees from African partner countries support the BfArM as visiting colleagues on a quarterly basis.



experts' know-how, but also have access to the BfArM's laboratories and devices.

However, the quality assurance and accreditation of state laboratories also play a central role in the field of drug monitoring. Within the scope of the project, the federal institute works together with the largest German monitoring laboratory, the Official Medicine Control Laboratory. "Here, our African colleagues can learn how to assess a laboratory's technical competency," explains Dr Stadler. "They can then use this expertise in their home countries and, above all, pass it on to others." Thus, the BfArM also makes a major contribution to the improvement of the pharmaceutical supply in the countries, in particular with regard to the drugs' pharmaceutical quality.

To be able to better adapt individual use of anti-infectives and in particular antibiotics to the patients, the federal institute is supporting three doctoral projects in Zimbabwe, Zambia and Malawi, which address individualised and rational therapy with anti-infectives in clinics specialising in infectious diseases. Accordingly, the BfArM

supports the training of young scientists in these countries to be able to prescribe therapeutic drugs in a more targeted way. For example, the individual dosage of a therapeutic drug for a particular patient can be optimised by monitoring the active agent concentration in the blood and examining individual profiles of drug metabolism.

But exact evaluation of interethnic differences in pharmacogenetics also plays an important role. How a person reacts to a therapeutic drug depends on his or her genetic makeup, among other things. This differs greatly among various ethnic groups – for example between Africans and Europeans. By taking this into account as far as possible in the treatment, the therapy will become more efficient. "As yet, it remains a challenging task to ensure the worldwide availability, quality and integrity of therapeutic drugs. By closely cooperating with the WHO, we are actively combatting the development of antimicrobial resistances together by pursuing bilateral programmes and setting up sustainable structures. Thus, we are strengthening the health care systems of our partner countries and therefore indirectly our own," emphasises Dr Stadler. "In doing so, we are supporting our African colleagues with the full expertise of our scientific staff."



# GCP Inspections: an important tool in patient safety

Experts from the BfArM travel all over the world as inspectors of clinical trials. Plenty of experience, an advanced level of expert knowledge and communication skills are particularly important for their work.

For a drug to be approved in the EU, it must first be tested on humans in clinical trials. According to the German Medicinal Products Act and European regulations, internationally recognised ethical and scientific standards of “Good Clinical Practice” (ICH GCP) must be complied with, from development via implementation through to the evaluation of a clinical trial. Compliance with these standards is intended to safeguard the rights and safety of participating patients, as well as to ensure that the data collected from the clinical trial is credible and valid. Clinical trials which are carried out outside Europe are held to the same standards as those carried out within Europe, if they are intended to be the basis of approval applications in Europe.

In order to monitor proper execution of clinical trials and the validity of the data collected, the BfArM, the Paul Ehrlich Institute (PEI) and state authorities – each according to their jurisdiction – carry out GCP inspections. The BfArM is hereby responsible for GCP inspections relating to the authorisation of clinical trials in Germany, as well as for GCP inspections relating to approval applications. These may take place in Germany, in the EU or in non-member countries. One of the BfArM’s inspectors is Dr Bärbel Witte, who has many years of experience in this field.

**Dr Witte, you have been working as a GCP inspector for the BfArM since 2004. What triggers an inspection and how are the inspections organised?**

GCP inspections are usually requested directly by the clinical assessors, or by the EMA in the case of central approval processes. We then approach the assessors to find out what concrete questions and concerns they have. Together, we decide where the GCP inspections can reasonably be car-

ried out. In some cases, certain questions can only be assessed on the sponsor’s premises – for example, if the assessors have concerns regarding processing of the acquired data and its analysis. More often, however, individual trial centres or laboratories are inspected. Simultaneously, we begin putting the inspection team together. As a general rule, we always have a second pair of eyes in the team, whereby the two inspectors usually come from different EU member states, if possible. In this way, we are constantly working together with our European colleagues. The European GCP inspectors are extremely closely coordinated, which means cooperation is always pleasant.

**The inspections are announced in advance – doesn’t this give the institutes enough time to conceal possible regulation violations?**

Of course, companies attempt to “tidy up” their paperwork before the inspection. But concealing any relevant regulation violations to the extent that there are no indications of them in the paperwork or in the interviews during the inspection is extremely hard, especially as all employees participating in the clinical study would also need to be suitably briefed. Additionally, during the inspection we verify data submitted for the approval process at the location where it was collected or processed. If the data has been retroactively altered or manipulated, this would be discovered on location, for example by comparison with medical records.

However, in order to further reduce the risk of cover-ups, we are moving towards also carrying out unannounced inspections or inspections with extremely short lead-times, whenever possible.

DR BÄRBEL WITTE

**Do you feel that the quality of clinical trials has improved over time thanks to the GCP inspections?**

The GCP inspections have definitely led to sponsors giving a higher significance to quality management of clinical trials. After the inspections, we often receive feedback from the sponsors' quality assurance departments saying that the GCP inspection helps them to implement improvements to the quality management of clinical trials.

**What is important during the inspections? What special skills do you need?**

As a starting point, GCP inspectors need to be scientifically trained and have a good knowledge and experience of implementation of clinical trials. Of course, we need to know and understand the purpose of the applicable regulations, in order to be able to decide how to interpret potential violations on a case-by-case basis.

Good communication skills and assertiveness are also important to be able to hold structured interviews and ask questions such that the required information is provided. We need to be able to convey any shortcomings to the inspected facility, the assessors and the CHMP. For this, it is necessary to write the inspection report extremely precisely and understandably.

As we work in a variety of international teams, a capacity for team work and an extremely good command of English are further requirements for a job as a GCP inspector.

**What appeals to you personally about the job?**

Personally, I find the variety exciting: with each process, we are able to familiarise ourselves with a new indication, and we always know what is currently being researched in the pharmaceuticals sector. We get to know new trial centres and companies and their work processes in each inspection. And working with European colleagues has its own special appeal.

**The value of GCP inspections in non-member states is often questioned in light of the large number of study centres there. What is your response to these concerns?**

GCP inspections are an extremely important tool and have regularly led to concrete measures to ensure patient safety in the past. One example: When GCP inspectors from the French medicine authorities discovered in 2014 that electrocardiograms had been falsified in several studies by an Indian contract research organisation, the BfArM reacted immediately and temporarily suspended approval in Germany for the affected drugs. This was a clear signal, both for the contracting authority and for the relevant contract research institutes, that manipulations of such studies will not be tolerated. It was shown here that the system fundamentally works. Defects are revealed and should thereby be avoided in the future.



# Clear standards for the approval of biosimilars

Cheaper copycat drugs, so-called biosimilars, have been developed for a number of biological medicinal products (biologics). Their approval requires particular standards, which the BfArM's employees had significant involvement in establishing in the EU.

While most medicinal products are manufactured using chemical synthesis, biologics are produced using material of biological origin. Usually, the desired active ingredient is produced by means of biotechnological changes to the cells used. Biosimilars are developed such that they are so similar to an already-approved biological medicinal product (the so-called reference product) that they can be used in place of the reference product. If the reference product's document protection has run out, the corresponding biosimilars can be approved. The importance of biosimilars will continue to increase in the coming years due to expiring patents. More and more patients will be treated with biosimilars, instead of having to rely on ex-

pensive biologics. In this way, biosimilars contribute to eliminating existing supply shortfalls.

In the approval process, certain particularities must be considered, as the active ingredients of biosimilars can slightly differ to those of the reference product. This can be explained by the fact that biologics have complex molecular structures and natural variability, as well as requiring a particular method of manufacture. "This means that a biosimilar cannot be completely identical to the reference product," explains Dr Brigitte Brake. She leads the specialist area "Pharmaceutical Biotechnology, Quality Inspection" at the BfArM, where scientific inspections of quality documentation for European and national approval processes for biologics take place.

Similarly to applications for generic drugs, the approval process for a biosimilar can refer back to a reference product. As described above, it cannot be assumed that the medicinal product in question is completely identical to the reference product, meaning that the applicant is obligated to provide much more comprehensive studies than is the case for generic products. "We must be able to guarantee that the slight differences do not affect effectiveness and safety," emphasises Dr Brake. In order to guarantee consistent quality, safety and effectiveness, the development and approval of biosimilars is highly regulated. As a regulatory authority, we set clear standards here to ensure safe patient supply."





The decision of whether this biosimilarity has been shown adequately is made by the regulatory authorities on the basis of all of the provided comparability studies. In particular, there is a focus on the structural and functional comparability to the reference product. “We require applicants to provide extensive direct comparative data,” says the head of the specialist area. “These must be based on highly sensitive analytical methods.”

Among others, insulin is one of the biological medicinal products for which biosimilars have been successfully developed. The approval processes for the indication “diabetes mellitus” are part of Dr Peter Mayer’s remit. He also believes that copycat biologicals will increase in importance in this area. “In recent years, companies have been able to heavily build on their experiences with biosimilars,” reports Dr Mayer, who also addresses safety-related concerns in the development of medicinal products as part of a research group at the BfArM. “It must be taken into account that the production of biosimilars is extremely demanding technically and can take several years”. For this reason alone, market penetration is still sluggish. “However, these products represent a safe alternative to the original products, not least because of the detailed investigation required during the approval process,” high-

lights Dr Mayer. In the field of diabetes treatment, three biosimilars based on insulin have now successfully gone through the approval process, two of them in 2017.

Since approval of the first biosimilars in the EU approximately ten years ago, the variety and sensitivity of the relevant analytical methods has increased greatly. “We

are already able to depict even extremely complex

biological substances better and better

and believe that high-definition

analytical methods will be available

to us in future, allowing

us to focus on addressing

the relevant quality aspects

for biosimilars,”

says Dr Brake. In order

to identify the

most suitable analytical

procedures and standardise

the evaluation of

biosimilars in Europe,

in October

2017 the BfArM

held a workshop for

assessors from all EU

member states. This

was on behalf of the European

Medicines Agency

and was attended by extremely

experienced experts from the

BfArM.

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In order to guarantee consistent quality, safety and effectiveness, this development and approval is highly regulated. As an approval authority, we set clear standards here to ensure safe patient care.

DR BRIGITTE BRAKE

# Supply shortages: The BfArM commits to transparency and dialogue

In response to supply shortages of medicinal products for human use, the BfArM pursues an improved flow of information and, in consultation with all parties, works to ensure patient supply is normalised as quickly as possible.

Where therapeutic drugs are not available at all or in the required quantity, this causes problems for all parties involved in healthcare. At the BfArM, a special expert team in Authorisation Division 1 has been working on this important issue for two years now. Here, all information on supply shortages is collected. Among other things, pharmacist Christiane Dahl is responsible for processing and following up on reports received by the authorisation holders. Since 2013, the Federal Institute has published all these cases on its website. “We fundamentally overhauled this service in 2017 with regard to user-friendliness, and have since then been providing the relevant information in a modern database application,” explains Christiane Dahl. “The reports are automatically processed and targeted searches in the database application can, for instance, be carried out for drug names, ATC codes and active ingredients.” In addition, the BfArM evaluates the reasons behind the supply shortages. “In about 70 percent of the cases, manufacturing problems are reported, and in about 25 percent of the cases, insufficient production capacities are given as the reason,” reports Dahl. “Quality deficiencies are also being mentioned more and more frequently.”

To be able to decide whether a supply shortage is “critical” or not, the team also works with several lists of active ingredients which are seen as particularly relevant for the supply of the total population. These were primarily selected by medical societies on the basis of the WHO list of

essential active ingredients. “Where a therapeutic drug linked to a special supply risk is reported, we will monitor this drug especially closely with a view to a reliable patient supply,” explains the Head of Authorisation Division 1, Dr Michael Horn. “We want to identify potential supply gaps as early as possible, in order to be able to act in a targeted manner. As a result of the modified procedure, we can now very quickly identify whether a reported supply shortage has the potential to be critical.”

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The common goal of all parties involved will continue to be normalising patient supply as quickly as possible in the event of shortages

DR MICHAEL HORN

These lists are regularly monitored by the BfArM with regard to the supply situation and are made available to the public on the BfArM’s website. The publication was recommended by our regular meeting on delivery and supply shortages. These meetings, which are also attended by the Federal Ministry of Health, higher federal authorities and expert groups, have been taking place regularly since the middle of 2016.



At the meetings, the participants assess the supply situation and jointly discuss how to proceed. “This way, we have regular communication on the relevant courses of action with all stakeholders,” emphasises Dr Horn. “Also, in the event of supply-related delivery shortages, we actively approach the companies in order to jointly identify solutions.” Additional concrete measures are also possible, such as priority processing of authorisation requests or applications for the modification of a therapeutic drug.

In the past year, a supply shortage was reported for the anaesthetic Remifentanyl, causing the BfArM to intervene. “In this case, we initiated direct contact with the producer concerned and the medical society,” reports Dr Horn. In doing so, the mutual agreement was reached that Remifentanyl was to be used in a more targeted way to bridge the supply gap. Furthermore, alternative drugs were agreed on. “According to our information, no necessary operations had to be postponed because of this supply shortage, as was initially feared,” underlines the Head of the Authorisation Division.

Another example: After an explosion occurred at a major manufacturer of active ingredients, there was a supply shortage of antibiotics with the active ingredient combination of Piperacillin and Tazobactam. In this case, the BfArM reacted immediately. “The consequences of the supply shortage were assessed by contacting all authorisation holders, and the Federal Ministry of Health, among others, was notified about this loss of production and further details,” reports Dr Horn. “The Ministry was then able to quickly determine a supply shortage in accordance with Section 79 (5) of the German Medicinal Products Act (AMG) on the basis of this and

further information.” This allowed the relevant authorities of the German States to permit a temporary deviation from the provisions of the Medicinal Products Act, so that treatment with drugs which are not authorised within the scope of the Medicinal Products Act became possible. In addition, medical societies developed and published recommendations on treatment alternatives for the event of Piperacillin/Tazobactam being unavailable.

This shows that constructive communication between all parties involved, both in the regular meetings and in specific cases, produces concrete results. At the same time, the additional information published on the website of the BfArM ensures even more transparency and improves the flow of information. “The common goal of all parties involved will continue to be normalising patient supply as quickly as possible in the event of shortages,” emphasises Dr Horn.



# Work at the PRAC: determining, evaluating and minimising risks

Increasingly, drug risks in the EU are analysed, addressed by appropriate regulatory measures and minimised on a European level. Experts from the BfArM make a significant contribution to this process, ensuring the supply of safe, effective medicines.

When drug risks are evaluated on a European level, data and expertise from all regulatory authorities within the European Economic Area feed into the process. In the relevant committees of the European Medicines Agency, this data is interpreted and discussed. Experts from the BfArM make a significant contribution to this process, ensuring the supply of safe, effective medicines.

New findings on the safety of medicinal products can arise over the entire life cycle of a medication, even a long time after the medication has been granted an authorisation. An important instrument in the identification of possible drug risks is the closely monitored evaluation of reports on suspected side effects. Other data from various sources, such as epidemiological studies, can also provide indications of possible risks. New scientific findings, too, can

lead to re-evaluations of a medication's risk profile. If a risk signal arises for a medicinal product which is approved in several or all EU member states, procedures are initiated on a European level for closer evaluation of such signals.

The Pharmacovigilance Risk Assessment Committee (PRAC) plays a central role in the evaluation and monitoring of the safety of human medicines. Scientists from all member states are represented in the committee. Dr Martin Huber and Dr Valérie Straßmann from the BfArM work at the PRAC, determining, evaluating, minimising and communicating drug risks. Alongside constant engagement with the newest scientific data, this is also accompanied by regular participation in committee meetings, which last for several days. Here, the PRAC discusses data on drug risks and undertakes a risk evaluation. At the end of the process, the committee make a recommendation on what should happen next with the medication. Depending on the type of authorisation held by the product, the PRAC's recommendations are passed on to either the Committee for Human Medicinal Products (CHMP) or to the Coordination Group for Mutual Recognition and Decentralised Procedures – human (CMDh) for approval.

**Dr Huber, you have been a member of the PRAC since 2012 and have, during this time, implemented numerous risk evaluation procedures, together with your European colleagues. What has been your experience of the process? Are the members able to quickly agree on a recommendation or are there sometimes debates?**

There are detailed documentation and data underlying the procedures, which need to be worked through and interpreted. The committee is also able to call in further



experts or request further statements from the relevant pharmaceutical company, if required. At the end of the process, the PRAC has a number of possibilities for minimising risk, ranging from a request to alter text in the product's professional information and package insert, to withdrawal of authorisation. It is not unusual for individual member states to make different assessments on this. However, the additional benefit of the PRAC is the exchange of views and the opportunity to call on the knowledge of experts from all over Europe. Via these discussions, our joint goal is to reach the best conclusion for patient safety.

**Dr Straßmann, what have your experiences been like in the five years you have been part of the PRAC as a deputy member? What are the particular challenges of the work?**

The evaluation of data on drug risks is frequently extremely complex. The data often comes from extremely heterogeneous and varied sources, which have sometimes been evaluated by different experts within the European network. At the end of the process, this data and its evaluations must all be entirely integrated and brought together into a final recommendation. In addition, data on drug risks is often not as high quality as one would wish for an evaluation. In many cases, there is no data from high-quality, randomised clinical studies available, which makes interpretation more difficult. In pharmacovigilance and also at the PRAC, we often work in situations where

there is only a small amount of high-quality data available and uncertainties regarding the robustness of the available data can never be entirely dispelled. Nevertheless, it is necessary to make the best possible decision with regards to patient safety, even when under time pressure and in circumstances of uncertainty.

**Dr Huber, are there processes which are particularly important to you?**

Naturally, processes regarding drugs which many members of the public know from their own experiences are followed particularly closely. One example would be the risk evaluation process for fluoroquinolone and quinolone antibiotics. This process was initiated by the BfArM in February 2017. The reason for this was reports of long-lasting and severely detrimental side effects. The PRAC is now reviewing whether further measures to minimise risk are required. Furthermore, the question must be answered of whether the risk of the above-mentioned severely detrimental side effects has an impact on the risk-benefit assessment. This particularly applies to the use of the medications to treat less serious infections such as acute bacterial sinusitis, acute exacerbation of chronic bronchitis or uncomplicated urinary tract infections. For this process, the PRAC wanted to hear how the public judged the risk of this group of antibiotics and therefore initiated a public consultation in the course of the process. This gave patients, doctors, chemists and scientists, among others, the opportunity to inform us of their viewpoint and experiences with these drugs.

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At the PRAC, we discuss the essence of the complex work done by our colleagues in pharmacovigilance and the BfArM. We know we can rely on their expertise and support at all times.

DR VALÉRIE STRASSMANN

**Some of the drugs addressed have been on the market for decades. Which new aspects are examined in the processes?**

We are not dealing with the first evaluation procedure on fluoroquinolones. The drugs' safety has already been evaluated several times, on both national and European levels, in various processes, which led to a limitation of indications for the products, among other things. In accordance with the recommendations made, the package inserts for patients and professional information for doctors were supplemented several times with safety-relevant information and advice on serious side effects, for example. This also included information on possible tendon damage. The current process newly addresses the persistence of some side effects, particularly those affecting the locomotor system, the nervous system and the sensory organs. All reports and other data relating to the relevant serious side-effects were thereby re-evaluated on a European level.

**Is the PRAC's work always orientated towards the evaluation of this type of concrete risk signal, Dr Straßmann?**

No, the members of the committee also address general topics to improve drug safety. The corresponding projects and activities are defined on a yearly basis in a so-called work plan. For example, I am part of a work group investigating the effectiveness of pharmacovigilance measures. If we review which of these measures successfully improve drug safety and why, we can derive the key to success for other measures. This in turn benefits patient safety. In

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A strong PRAC which efficiently performs its duties can make an important contribution to patient protection.

DR MARTIN HUBER

In addition, the PRAC concentrates on epidemiological questions, for example approval and evaluation of the non-interventional epidemiological studies requested for the evaluation of drug risks (so-called safety assessments after authorisation). We are able to draw on the epidemiological expertise of the BfArM in this area, where we have a special area of focus in the pharmacovigilance department.

**Dr Huber, what other focus areas are there in this context? How can the PRAC's work be further improved?**

In fact, we are continually in the process of making our work more effective. For this purpose, we take a thoroughly critical look at the process workflows at the PRAC. Together with a Dutch colleague, I lead a project on improving processes, which we actively promote with other members, also in the context of a Work Plan. Feedback from our stakeholders on our methods is also important in this context. A strong PRAC which effectively performs its duties can make an important contribution to patient safety. The reliability and plausibility of the PRAC's recommendations have a decisive role to play here.

**Dr Straßmann, in 2017 the PRAC carried out its first public consultation within a risk assessment process. Those affected were invited to share their experiences with drugs containing Valproate with the committee. These drugs are used to treat epilepsy, bipolar disorders and, in some EU member states, migraines. Use during pregnancy, however, can lead to congenital malformations and**

**developmental disorders among children. Was that the reason for this new form of patient involvement?**

The last change to pharmacovigilance laws in 2012 created the option of public consultations at a European level. Through this type of consultation, the aim is to improve the participation of EU citizens and patients in decision-making processes. The Valproate consultation was the first European public consultation of this type. The risk assessment process for Valproate, which began in March 2017, was intended to clarify whether additional restrictions on use were necessary, given the risks which had been extensively evaluated in previous processes. It also addressed the question of whether there was a need for further information and clarification. The PRAC deemed it necessary to take the viewpoints and experiences of the EU public into account during the evaluation, which is still underway. The aim is to further optimise the existing risk minimisation measures.

**The service received an extremely positive response from patients and stakeholders and participation was high. Many of those affected reported on the impact that the use of Valproate has had on their lives, some extremely emotionally. How can consultations of this type help the PRAC with its work?**

In particular processes, it is important for the PRAC to obtain feedback and viewpoints from all the relevant and affected parties, in order to be able to reflect and take account of this in the evaluation process – such as here with Valproate. This then includes not only the viewpoints of the pharmaceutical companies, experts or committees of those in medical professions, but also those of the patients. The personal experiences and statements of patients and stakeholders, as those who are eventually directly affected, can be extremely helpful for this, and, as in the case of Valproate, introduce additional aspects of past or possible future risk minimisation measures, helping the PRAC with its final decision-making process.

**Dr Straßmann, Dr Huber, you both work on extremely complex procedures at the PRAC. How should we envisage the evaluation of the detailed information and data, which starts even before the meetings?**

**Dr Martin Huber:**

It is important to emphasise that the PRAC's work does not only represent the work of its members. At the PRAC, we ultimately present the results and conclusions of all the employees of the pharmacovigilance department and the BfArM at a European level.

**Dr Valérie Straßmann:**

At the PRAC, we discuss the essence of the complex work done by our colleagues in pharmacovigilance and the BfArM. We are dependent on their expertise and support and know we can rely on it at all times. Our commitment to the PRAC would be unthinkable and unmanageable without this teamwork.



# BfArM actively combatting counterfeit drugs at an international level

All in all, the number of identified cases of counterfeit drugs in the legal distribution chain is at a low level. Nevertheless, each case of counterfeiting can present severe risks for the consumer. The top priority is therefore to keep the distribution chain safe and ensure that all counterfeit drugs are discovered at an early stage.

According to the German Federal Criminal Office, the trade in counterfeit drugs has become an extremely lucrative branch in the world of organised crime.

The World Health Organisation (WHO) defines counterfeit drugs as medications that have been falsely labelled with a fraudulent intent. For instance, counterfeit drugs may contain an incorrect dosage of the active ingredient or none at all. The pharmaceutical quality of the drug is also not assured.

It is of the utmost importance for patient safety that all authorities continue their intensive cooperation in this area in future, in order to combat trade in counterfeit drugs as efficiently as possible. The BfArM plays a very important role in this cooperation: It coordinates the flow of information between the authorities and bodies involved and provides information to the public.

Once counterfeit drugs have been identified, the prosecution itself is pursued by the police, the public prosecutors' office and customs. The responsible higher federal authorities (BfArM, Paul Ehrlich Institute and the Federal Office of Consumer Protection and Food Safety) are responsible for

the central collection and evaluation of the risks occurring if these drugs are consumed, as well as for the coordination of the necessary measures for consumer protection. The BfArM maintains its own division with specialised employees especially for this function.

“Contact with colleagues at an international level is part of our daily routines,” says

Dr Jörg Dussa, the Head of Unit:

“Counterfeiting often goes hand in hand with concealment of the distribution channel, which may involve many different wholesalers in various countries.” For patient protection, the international networking of the authorities is therefore of particular importance. This allows important information to be passed on swiftly.

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Counterfeiting often goes hand in hand with concealment of the distribution channel, which may involve many different wholesalers in various countries.

DR JÖRG DUSSA

To forward this information, the authorities work with so-called rapid alert systems. These systems enable them to quickly notify the EU medicines agencies

(such as the medicines agencies of the Member States, the European Medicines Agency (EMA) or the European Directorate for the Quality of Medicines) as well as international authorities like the WHO about counterfeit drugs and keep them up to date in current matters. “Apart from this efficient rapid alert system, direct exchange with the parties concerned always plays an important role,” says Dr



Dussa. “The BfArM is active on many levels to take joint action against counterfeiting, in cooperation with its colleagues.”

For the protection of the legal distribution chain, it goes without saying that the intensive networking of all German authorities is also very important. In the unit, Dr Marcus Wittstock is responsible for communication via the rapid alert system as well as for exchange of information in the relevant workgroups. “We are in contact with the state authorities responsible for monitoring the legal pharmaceuticals market in Germany, as well as with prosecution authorities such as the Federal Criminal Office and the Customs Investigation Bureau,” he reports. An important group in this context is the Working Group of Enforcement Officers (WGEO), which is already ten years old and which the BfArM also belongs to. Its objective is the protection of public health against harmful medicinal drugs – in the areas of human and veterinary medicine alike. The WGEO is headed by representatives of the responsible medicines agencies in the EU; in addition, the group also includes representatives of the national police and customs authorities. The members come from all Member States of the EU and the European Economic Area. Among its partner organisations are the EMA, Europol,

Interpol and the WHO.  
“The WGEO has thus created

a network and a rapid alert system which can be used to exchange confidential information on counterfeited or stolen drugs,” explains Dr Wittstock. “Furthermore, the members meet every six months, including training based on specific case studies.“

In order to improve communication and coordination between the relevant national authorities even further, a database for counterfeited medicines has been developed under the leadership of the BfArM. This database was ready for presentation to the relevant national authorities in the first quarter of 2018. It contains confidential information and is used by the authorities alongside the already established communication channels to research, analyse and assess current, or in some cases even older, counterfeiting cases.

With a view to combatting counterfeited drugs, the implementation of the so-called counterfeiting directive is a further important step. Among other things, the directive specifies that from 9 February 2019, virtually every pack of prescription drugs must be equipped with a specific identifying feature. Before the drug is handed out to patients, the unique barcode on every single pack is scanned and reconciled via a database. This way it can be determined whether the pack is valid and whether the drug contained is genuine.

All the above measures aim to as far as possible prevent the intrusion of counterfeited drugs – including stolen drugs – into the legal distribution chain in future, and thus to make a substantial contribution to patient safety.



# Antibiotics: reducing the risk of resistances through proper use

The BfArM has long promoted the publication of an adequate picture of the current antibiotic resistance situation in summaries of product characteristics and is thus making an important contribution to improving appropriate prescription and use of antibiotics.

“The knowledge of the current resistance situation is crucial for the proper use of antibiotics!” This is one of the key statements of the BfArM experts who are committed to taking up the battle against antibiotic resistances at a national and international level. Sibylle Matz, for instance, has been active in various committees and projects for many years now, with the aim of containing the further spread of antibiotic resistance, both nationally and internationally. At the BfArM, she heads the “Infectiology/Dermatology/Allergology” Unit in the Authorisation Division 3. The Federal Institute acts as part of a network of researchers, independent experts and representatives of scientific societies and the pharmaceutical industry.

Antibiotics are indispensable for the treatment of infectious diseases. However, pathogenic bacteria around the world are becoming increasingly less vulnerable or even resistant to many authorised antibiotics used in human and veterinary medicine. In Germany, there are currently about 2000 medicinal products with systematic antibiotics on the market for human use – in addition to many other anti-infectives (such as antiviral and antifungal drugs). “The proportion of pathogens resistant to antibiotics is, however, steadily increasing,” reports Sibylle Matz. “As a result, the treatment of infectious bacterial diseases is a rapidly growing problem.”

The resistance situation differs from pathogen to pathogen: Whilst resistance rates to antibiotics are currently relatively stable for Gram-positive bacteria and are even slight-

ly declining in some countries, the resistance rates for Gram-negative bacteria are rising throughout Europe.

“Although a few new antibiotics against Gram-positive resistant bacteria have been authorised over recent years, we are currently still lacking new active substances against Gram-negative bacteria,” Matz describes the situation. “This is a danger to public health.” Annually, up to 600 000 patients become infected in Germany during in-patient treatment. Up to 15000 of these patients even die from these infections. “At least one third of these infections could be avoided,” estimates Sibylle Matz. “To achieve this, it is necessary to constantly ensure hygiene in hospitals and proper use of antibiotics.”

## The German Antibiotic Resistance Strategy 2020 (DART)

In cooperation with the Federal Ministry of Food and Agriculture and the Federal Ministry of Education and Research, the Federal Ministry of Health developed the German Antibiotic Resistance Strategy 2020 (DART) which was approved by the German Federal Cabinet in May 2015.

DART 2020 brings together the necessary measures to achieve a reduction of antibiotic resistances, whereby cross-sectoral cooperation (one-health approach) has top priority. In order to meet all requirements of the one-health approach, all targets of DART 2020 strategy address both human and veterinary medicine.



SIBYLLE MATZ

International studies show that in up to 50 percent of applications, antibiotics are prescribed in inappropriate doses or over an unsuitable period. This improper prescription and use of antibiotics is the main cause for the rise in antibiotic resistance. It is therefore particularly important that the attending physician is provided with valid and current information on the concrete resistance situation to ensure proper application of each and every antibiotic. Accordingly, the BfArM focuses its activities in particular on the proper use of antibiotics, which can be inferred from the current information provided in summaries of product characteristics. “Consideration of current information on the concrete resistance situation is a vital prerequisite for ensuring that an antibiotic maintains its effectiveness for as long as possible,” emphasises Matz.

To achieve this, the BfArM has among other things initiated a project unique in the EU, the so-called Central Office for the Evaluation of Resistance Data on Systemic Antibiotics (ZARS). This project has been collecting and evaluating all suitable data available in Germany relating to the resistance situation of about 50 systemic antibiotics on an annual basis since 2005. The BfArM strives to ensure that the current resistance situation in Germany and

the limit values for clinical sensitivity are adequately represented in the summaries of product characteristics of the relevant drugs. In the event of a change to the current resistance situation, Section 5.1 of the summary of product characteristics will be updated for the relevant pathogen, in order to enable proper use of the antibiotic by physicians. “Unfortunately, however, many physicians are unaware of the summary of product characteristics or make insufficient use of the information provided,” says Sibylle Matz.

In addition, the BfArM supports the German Antibiotic Resistance Strategy (DART), updated in 2015 by the Federal Ministry of Health (BMG) in cooperation with other Federal Ministries to “DART 2020”, in many other projects. Among other things for example, the BfArM plays an active role in the “Global Health Protection Programme” of the BMG (also see Page 10).

The objectives of DART 2020 also include supporting research addressing the reduction and control of antibiotic resistances, supporting the development of new antibiotics and the evaluation of older, known antibiotics for new indications. Here, Sibylle Matz’s unit is involved in national and European projects such as cooperation with the German Centre for Infection Research (DZIF). The BfArM’s experts provide regulatory and professional consultation on research projects in their very early translational phases and, in doing so, support the targeted development of new treatments for infectious diseases.

In this way, the BfArM is making an important contribution to improving proper prescription and use of anti-infectives and thus to containing further development of antibiotic resistances.

# Working at the BfArM: actively promoting health in Europe

The Head of Administration at the BfArM, Dr Ralf Halfmann, talks about the largest European medicines agency as an employer, internationally networked research for “safer health care” and interesting further development opportunities for employees.

Promotion of patient protection and new forms of treatment within a European network: The BfArM offers committed experts an exciting working environment. The institute has long since started to compete on an international level for the brightest minds – and is able to win over applicants with its many advantages. No matter whether physicians, IT specialists, engineers or administrative professionals: Working at the BfArM not only provides interesting further development opportunities in a stable working environment, but also offers many ways of actively promoting a safe and reliable supply of therapeutic drugs to patients.

**“Working in public service”: What would you tell potential job candidates who have never thought of switching**

**to the BfArM from a position at a clinic, in the industry or a scientific institution, Dr. Halfmann?**

Whenever we actively approach people for personnel recruitment, we do indeed often experience that experts from various work areas no longer have an up-to-date view of what “working in public service” really looks like. When talking with them, candidates often have a “eureka” moment, when they get a better idea of the way we work and the nature of our activities. Take the European authorisation procedure for new therapeutic drugs for instance. Here, we are talking of no less than the opportunity to help shape the healthcare of tomorrow. Our experts work in prominent positions in European expert groups, assess the opportunities and risks of new therapeutic options and, in doing so, are in the position to set the right course internationally. As the largest European medicines agency, this makes us one of the key stakeholders when it comes to giving new impetus in the area of patient care, together with a network of other authorities. Solely on the basis of our professional competence, we offer an attractive working environment for physicians and pharmacists, for example – to say nothing of the further benefits of a secure position with lots of further development opportunities.

**What features must a contemporary personnel recruitment concept have, in order for the BfArM to attract attention and win potential applicants over in the competition for the brightest minds?**

We must be able to react quickly to changing conditions on the recruitment market.





Today, we are one of many employers providing jobs – or depending on the perspective, seeking candidates – on the job market. This makes it so important for us to proactively present our organisation and make all facets of working at the BfArM visible, in order to be considered as an attractive employer by our potential “clients”, the job applicants. The days when a public employer was able to draw on unlimited resources are long gone. Particularly in some highly skilled professions, there is clearly a demand surplus. And it cannot be expected that the situation will change again in the medium-term. Moreover: We are not only in direct competition with the industry when it comes to recruiting the brightest minds, but also competing with a whole array of other authorities in Germany and Europe. As a public employer, we have the same financial instruments available as the other authorities. The basic and starting conditions are therefore identical. We can, however, win applicants over with a few special perks of working at the BfArM. Above all, this involves interesting and important activities in the area of healthcare, offering opportunities for further development, an attractive working environment and excellent working conditions. In general, our employees stay employed at the BfArM on a long-term basis, so we have extremely low staff turnover. This proves that we are sustainably attractive as an employer. However, we need to act even more proactively in order to address candidates in

the first place, start establishing contacts at an early point and make our activities and the benefits of the BfArM as an employer as transparent as possible for successful recruitment. We have therefore set ourselves the objective of responding to the requirements of today's generation of applicants even more flexibly in the future.

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Our experts work in prominent positions in European expert groups, assess the opportunities and risks of new therapeutic options and, in doing so, are in a position to set the right course internationally.

DR RALF HALFMANN

**What does the active involvement of the candidates in European drug safety mean, in concrete terms?**

Patient safety is our top priority. For this reason, we successfully communicate our critical view and our high safety requirement in numerous European committees.

When we discover new drug risks, we initiate effective measures. This is what we do in the Pharmacovigilance Risk Assessment Committee (PRAC) at the European Medicines Agency (EMA). The PRAC ensures that the expertise and resources required for the assessment of drug safety related issues at EU level are available. Specifically, our representatives in the PRAC strive to ensure that newly identified risks are scientifically assessed and that patient safety measures are initiated and implemented, where necessary.

**How important are research and science for the work of the BfArM?**

As a federal and departmental research institute we deal with safety and efficacy issues directly related to the pa-



tients. In this context, our distinctly scientific profile supports the whole spectrum of the BfArM's scientific expertise in its regulatory core competencies. This results in intensive communication between the regulatory divisions and our research groups. On top of this, we also maintain numerous partnerships with universities and other scientific institutions. One example is drug therapy safety management: Within the scope of the ADRED research project, we are investigating all emergency admissions of patients in three clinics to assess whether their situation results from erroneous prescription or use of therapeutic drugs. Researchers at the BfArM want to thus gain new insights on the extent of and reasons for medication errors, in order to develop improved strategies for their avoidance.

#### **What opportunities for further training and development can you offer employees?**

Due to our function as an authority working in the field of science, the continued further training of our employees is crucial for us. In general, our employees can take part in all further training and development programmes and courses which are deemed appropriate and required for their professional career. Apart from a whole array of in-house training programmes, we also offer many courses by external providers across the public and private sector. With regard to further development opportunities, however, we have a little less freedom than in the private sector. Nevertheless, especially for young professionals, we can offer excellent further qualification and development options, leading right up to executive positions. In addition, we offer many advantages such as long-term employment and family-friendly and flexible working-time models. Furthermore, the healthcare sector is a relatively large business segment with a variety of international relations. The BfArM's experts are represented in many national and international committees, for example in workgroups of the European Commission, the European Medicines Agen-

cy, the European Council and the WHO. For the promotion of additional career development opportunities, we also offer a special kind of personnel rotation known as "procedure-based rotation". This enables our employees to familiarise themselves with procedures applied in other units on a fixed-term basis, without having to change their job. This not only gives our staff a broader view of matters, but also strengthens their scientific competencies.

#### **What personnel development programmes are there, for example for potential executives?**

At the BfArM, both future and currently active executives must offer a high level of methodical, social and personal competencies, coupled with strong leadership skills. To meet these requirements, we take particular care to support the continuous and systematic further development of their leadership skills. In addition to the personalised support provided by Personnel Development with selection and attendance of seminars for training basic leadership skills, we also offer comprehensive in-house courses on communication skills and advanced seminars, for example on the management of personnel in mobile and teleworking positions, personnel recruitment interviews, job specifications, personnel management on a part-time basis and various courses on health topics. At regular intervals, we conduct executive feedback surveys to maintain and optimise good leadership behaviour and the communication between executives.

#### **What does a speciality training course for physicians involve and what requirements must be met?**

With the exception of the clinical part of the training, physicians can complete their entire 48-month speciality training in clinical pharmacology at the BfArM. This includes basic further training in "Pharmacology and Toxicology", as well as the specific part of the speciality training in "Clinical Pharmacology". In their daily work at the institute,



KERSTIN ZÄPFEL

junior experts become familiarised with the contents of the speciality training, flanked by expert seminars. In our research and analytical laboratories, junior experts also have the opportunity to learn and expand their knowledge in analytical methods. To participate in the speciality training programme, you must be licensed to practice medicine, and 12 months of work experience in clinical medicine is beneficial but not mandatory for acceptance to the speciality programme. Later, however, this work experience is a mandatory requirement for taking the specialist examination, although it is possible to complete the work experience within the scope of partnership programmes with the University of Bonn.

#### **How does the BfArM support the reconciliation of family and job?**

In the summer of 2016, the BfArM was awarded the certificate of the “berufundfamilie Service GmbH” for the second time. This award was the result of a successfully completed re-auditing process. The team of auditors expressly praised our endeavours in many areas. In particular, our teleworking and mobile working jobs were widely acclaimed. The tools developed by us to enable more flexible working hours, e.g. a voluntary option to work on

Saturdays due to family responsibilities during the week, long-term transferability of extra work and overtime as well as the introduction of long-term working time accounts were also highly commended. We also attach great importance to the factor of “Leadership at the BfArM” in connection with the reconciliation of family and job. In this context, we have, for example, implemented models in which executive positions can be held by several people, employed on a part time basis. At the same time, we specifically train our executives in reconciliation issues.

#### **Let’s talk about the recruitment of young talent: What role does vocational training play at the BfArM?**

At the BfArM, vocational training is one of the key pillars for targeted qualification of the employees of tomorrow. And this is no longer simply a matter of purely subject-focused vocational training. Our new Head of Vocational Training, Ms Kerstin Zäpfel, also strives to consciously promote the development of professional and interdisciplinary key qualifications for young people, such as methodical expertise and the ability to act on their own initiative. The range of vocational training programmes on offer is broad and reaches from administrative clerks via specialists for media and information services and chemical laboratory assistants to IT specialists. After successful completion of their training, many of our 50 trainees will find permanent employment at the BfArM. In the vocational training area, we are also implementing new employment models: To promote the reconciliation of family and job, we offer the opportunity to complete vocational training on a part-time basis – for instance, in cases where the trainee is also caring for children or other family members living in the household who are in need of care. This allows us to offer interesting job opportunities in all kinds of work areas, which accommodate our staff’s personal living situations in a contemporary way.

# Shaping health: health management at the BfArM

Apart from their proven professional expertise, the motivation and health of the BfArM's employees are among its most important resources. For this reason, "Good work in good health" is the motto of the Health Management unit at the BfArM.

Only with committed employees can we succeed in actively shaping health in Europe. Professional expertise alone is not enough for this purpose. No matter whether you are a doctor, pharmacist, administrative clerk or lawyer: the health and motivation of the employees are key factors in the BfArM's success. This is why the BfArM not only stands up for the health of its patients but also promotes the health of its staff. "The company health system at the BfArM helps ensure that all staff members are able to produce good work in good health – while taking into account their personal stage of life and the principle of inclusion," Dr Hieronyma Schell outlines the goals of her work. As a physician and the head of the Health Management unit, she knows precisely how important measures are which are tailored to the actual needs and requirements of the staff and which actually make it to them.

The BfArM concept provides for a systematic approach, in order to be constantly able to react to all developments. For instance, the superordinate fields of activities of the BfArM Health Management unit are determined in regu-

lar staff surveys. The process, involving analysis as well as the planning, implementation and evaluation of measures, is continuously pursued. The practical implementation involves measures from the areas of both conditional and behavioural prevention.

Conditional prevention measures aim to create a positive impact on the health of the employees by changing conditions, in this case working conditions. An important example of this are our health circles. These are temporary workgroups made up of our employees, whose objective it is to analyse any working conditions with a potentially negative impact on health and to develop suggestions for improvement. "The underlying concept behind these health circles is that the employees are the best experts on their own work situation and know best

where the problems lie and what remedies are viable," Dr Schell outlines this approach. At the same time, these circles can also contribute to identifying a "Best Practice" approach and establishing which existing working conditions are deemed as especially supportive

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The company health system at the BfArM helps ensure that all staff members are able to produce good work in good health – while taking into account their personal stage of life and the principle of inclusion.

DR HIERONYMA SCHELL

by the employees and, ideally, how these conditions can be transferred to other units.

A further key element of conditional prevention are executive seminars. “This specifically enables our executives to identify requirements in their units, to enter into a dialogue with their staff and to provide solutions,” says Dr Schell. The range of topics is as broad as the range of requirements in day-to-day work. Not only executives benefit from topics like “Healthy and resilient leadership”; all staff members will ultimately enjoy the advantages. Further examples for conditional prevention measures include ergonomic office equipment and healthy canteen catering.

In contrast to the conditional prevention measures, the area of behavioural prevention primarily deals with topics that can ultimately only be influenced by the individual staff members themselves, by changing their own behaviour: sufficient exercise, a healthy diet and dealing with mental stress. To prevent a lack of exercise, for example, the employees of the BfArM can go on outdoor courses or “active breaks” at lunchtime. In back workout courses, they have the opportunity to learn targeted corrective exercises in response to their work at the computer screen, which they can then also carry out at their workstation for quick relief. In order to be able to deal better with – inevitable – stress, the BfArM offers special resilience seminars for its employees. Participating employees also benefit from these behavioural prevention programmes beyond working hours. A thoroughly desirable “side effect” of the company health management programme.

At the BfArM, “looking after” the health of all employees is understood not as the exclusive responsibility of the Health Management staff, but on a holistic basis. For this reason, the Health Management unit is now integrated with the



personnel division. This enables the pursuit of staff health as a key element of the BfArM’s personnel strategy and as a cross-sectional task which is taken into account in all areas of activity. “We want to show that the institute’s management board, our executives and all employees are jointly committed to their responsibility for the health of all staff members in terms of an appreciative approach,” emphasises Dr Schell. For this reason, Health Management collaborates closely with further units of the BfArM, which specifically promote the health of the employees in different areas such as the occupational safety unit, in-house medical services and social counselling. A clear advantage for employees, who can claim personal counselling or support in many different work and life situations within the scope of this holistic health management programme.

# Facing the challenges of tomorrow today

The BfArM has established a department to address the issues of “Demographic Change” and “Knowledge Management” and started to develop early concepts in these areas. In this interview, the Head of the unit, Ulrich Meyer, and Lilian Pfender talk about how to deal with foreseeable change processes.

## Mr Meyer, what challenges do you believe the BfArM will face in light of demographic change?

The average age of the employees at the BfArM is about 47 years. More than 130 of our nearly 1100 employees will reach the age of 65 within the next 5 years, or in other words, 12 percent of the staff will retire in the near future. The demographic change in Germany with an increasing number of older people – in 2015, the average age of the population was 44 years – and the decline of the working age population has an enormous impact on society and on the labour market. This situation is also making itself felt at the federal institute. The changed age structure of the employees, the growing number of retiring staff members, the potential loss of expertise and the lack of junior staff and specialists are challenges to which the BfArM began reacting a few years ago.

## Mr Meyer, what options does an authority have to prepare for such change processes?

Very much in the spirit of the demography strategy of the German federal government, we strive to think and act across all generations. On the one hand, the employees and their expertise are a key success factor: Our employees are our greatest asset, their specific expertise protects patients while at the same time ensuring our strong position in Europe. With the retirement of experienced personnel, there is a risk of their expertise being lost, as new staff members will naturally not have completely identical professional knowledge at their fingertips. In our “Organisation, Knowledge Management, Library” unit, we approach this challenge by introducing intergenerational knowledge management. On the other hand, we are also focusing on demography-orient-

ted personnel management, partnerships with universities and lifelong learning in the areas of training, further training and specialist training. Last but not least, we support the reconciliation of work and family and have launched a Health Management unit. These measures are not only intended to maintain the working capacity of experienced employees, but also address new qualified candidates. By offering attractive intergenerational working conditions, we have managed to increase the number of recruitments and reduce the average age of the BfArM staff from 50 years in 2013 to 47 years in 2017.

## Ms Pfender, what do the solutions implemented at the BfArM look like in practice?

To be able to react to the foreseeable decline in experts, we rely on a combination of knowledge transfer and a precautionary demographic personnel policy: For the 2017 personnel budget, the BfArM made successful use of the option of introducing overlapping jobs. This means that experienced job holders will help to train their successors themselves over an adequate period before retiring. In future, the need for these posts will be determined by the information provided by our personnel management system on age-related fluctuation.

Apart from the personnel management system, expertise at the BfArM is also secured, expanded and distributed by means of other measures and methods.

A fundamental example for this is the Intranet as a basic means of internal communication of knowledge management. In addition, we publish







Our employees are a key success factor, as their specific expertise protects patients and ensures our strong position in Europe.

ULRICH MEYER

expertise on the BfArM homepage and in the specialised scientific library, as well as in the electronic document management and case processing system.

Moreover, we have setup a learning platform in cooperation with the Federal Academy of Public Administration (BAKöV), for which we are developing individual study modules for the various units. This enables users to interactively further develop their knowledge directly at their own workplace. One of the primary users of this learning and knowledge management system is our own research department, together with whom we have already created e-learning programmes on research projects, such as for instance the “Ubiquitous Pharmacogenomics (U-PGx)” or the “Global Health Protection Programme (GHP)”.

Finally, when employees retire, there is also the possibility to determine which expertise should be secured and transferred in expert interviews and by intermediary moderation. This is achieved by means of an automated notification procedure which reminds us about upcoming retirements at an early stage.

**How do you deal with the requests and expectations of the employees who are associated with the demographic development, Ms Pfender?**

For one, it is important to recruit new personnel. On the other hand, it is vital that the existing employees identify themselves with our federal authority – and stay employed with us in the long-term. As life expectancies and age thresholds for retiring are generally rising, we support our employees with our Health Management programme, for example by offering presentations, in-house sports facilities, training courses or e-learning. Furthermore, we react to our employees’ wishes for workshops on health or the reconciliation of work and family – whereby the motivation and the appreciation of staff members of all ages are essential.

In addition, our employees are involved in a certified family- and life-phase-friendly personnel policy, enabling them to reconcile their job and their career with their family life and caring for children and other relatives in need of support. Accordingly,

we offer part-time jobs, flexible working hours and approximately 200 teleworking jobs, as well as mobile working options. The fact that our institute is considered to be a flagship for the reconciliation of work and family within the “work and family audit” certification helps us recruit qualified junior employees as well as specialists and executives. Also, we calculate staffing requirements which not only focus on quantity planning, but also take into account the requirement for professional expertise, in particular with regard to scientific staff.

**Let’s consider the aspect of company - or in this case authority - culture: how do you prepare executives for these new challenges, Mr Meyer?**

The executives must approach these changes with foresight. They must simultaneously ensure that the high performance level of the BfArM in terms of patient protection is constantly maintained. For this reason, we work together with the in-house personnel development unit to offer training courses that deal with the topic of demography in management culture, for example “Healthy and appreciative leadership under demographic change” or “Leadership on a part-time basis”. In addition, we test out new management models, such as double staffing or filling positions with a different share of working hours. This enables our staff to reconcile an executive position and a career with their family life and promotes both teamwork between junior and senior staff members and rotations to different areas of activity. But what ultimately counts, is the role model function of the executives: the executives should motivate their staff to further develop their expertise and maintain a healthy lifestyle, lifelong learning and a transfer of knowledge.

# Cannabis Agency established for future cultivation of cannabis

In March 2017, national legislature expanded the options for prescribing medicinal cannabis products and when this law took effect, the BfArM established a Cannabis Agency.

In 2017, national legislature expanded the options for prescribing medicinal cannabis products by passing a law amending provisions under the Narcotics Law and other regulations. Physicians can now officially prescribe medicinal cannabis products. In doing so, however, they must comply with the relevant requirements under Pharmaceutical and Narcotics Law. In addition to the new provisions, the previous treatment and prescription options for the relevant finished medicinal products and prescription drugs will continue to be available.

At the same time, the German Cannabis Agency started up its activities at the BfArM. In the medium term, the availability of cannabis for medicinal purposes should be ensured by means of cultivation in Germany. In accordance with the United Nations Single Convention on Narcotic Drugs of 1961, a Member State must establish or appoint such a public agency as soon as cannabis is intended to be cultivated in the state in question for non-industrial uses. The Agency will manage and monitor the cultivation of cannabis for medicinal purposes. Head of the Cannabis Agency is Prof. Dr Werner Knöss, who addresses this topic together with colleagues from the “Complementary and Alternative Medicines” Division at the BfArM.

**Prof. Knöss, the Cannabis Agency is entrusted with the task of contributing to supplying patients with pharmaceutical grade cannabis produced in Germany in the medium term. Achieving this objective, however, initially requires developing completely new structures and making decisions for which no previous experience can be drawn on in Germany. What challenges have you had to deal with in this context to date?**

One of the major challenges is undoubtedly making long-term decisions without being able to rely on pre-existing regulations or experience. However, we had naturally already been in contact with a number of experts before the law amending provisions under the Narcotics Law and other regulations came into force. But of course, we also had to implement certain things in Germany for the first time – starting with a procedure to select suitable companies to be assigned by the Cannabis Agency to cultivate cannabis. In this case, we also had to react to a court order in the meantime. We strive to thus bring the process to a sustainable solution and play our role in ensuring a safe supply for patients.

**What functions will the Cannabis Agency assume as soon as the cultivation of cannabis has begun in Germany?**

The functions of the Cannabis Agency are based on the requirements set out by the Single Convention. We monitor the cultivation, harvest, processing, quality assurance, storage, packaging and the distribution of cannabis to wholesalers and chemists or manufacturers. In this context, we must repeatedly stress that the cannabis is not cultivated by the BfArM itself, but by the commissioned companies. Even when we purchase the harvested cannabis, the harvest is not transported to us, stored at the BfArM or distributed from here. These steps will be carried out by the relevant producers or other commissioned companies. The Cannabis Agency as the responsible pharmaceutical entrepreneur must ensure that only pharmaceutical grade cannabis is supplied to chemists. In doing so, the relevant requirements based on the underlying legal framework and the corresponding guidelines must

PROF. DR WERNER KNÖSS

be complied with. Cannabis for medical purposes is naturally also subject to the provisions of the Narcotics Law.

**You referred to the pharmaceutical grade of the cannabis which must be ensured by the work of the Agency. Which specifications will you follow in this regard? This type of cultivation is as-yet unknown in Germany.**

In the matter of cultivation, prior to the tender process we were already in contact with other countries in which cannabis has been cultivated for years under state control. We wanted to benefit from the experiences gained in these countries and get a concrete on-site impression of the conditions under which cannabis is cultivated there. It should not be forgotten that the cannabis required by us is a medicinal product, for which, among other things, it is mandatory to prove the pharmaceutical grade of the cannabis as required by the pharmacopoeia. Before the law amending provisions under the Narcotics Law and other regulations came into force, there was not yet a monograph reference in the pharmacopoeia, meaning that the BfArM had to prepare the monograph in a very short period of time. The monograph is a very important quality assurance instrument and constitutes an essential requirement for chemists and the pharmaceutical industry. And above all, our work contributes to improving the supply for patients.

**What conclusions would you draw at this point?**

Supplying patients with medicinal products of an established pharmaceutical grade lies at the centre of our work. The law is an important step forward for severely ill patients for whom medicinal cannabis products may be an advisable therapeutic option.

For the BfArM, the work of the Cannabis Agency is an overall project within the scope of which the expertise of the entire organisation needs to be merged. Together, we will make a contribution to supplying severely ill patients with pharmaceutical grade cannabis.



# Cannabis as medicine: the important role of the Federal Opium Agency

Since March 2017, physicians have the option of prescribing medical pharmaceutical grade cannabis flowers or cannabis extract using special prescription forms. This has been made possible by a corresponding law amending provisions under the Narcotics Law and other regulations.

Previously, it was not permitted to prescribe cannabis flowers and extract, meaning that it was only possible to take cannabis for medicinal purposes as a form of self-therapy under the supervision of a physician. In this case, purchasing cannabis flowers and extracts required a special authorisation issued by the BfArM in accordance with the Narcotics Law. Since there it was not possible to have the expenses incurring refunded by statutory health insurance, there were cases in which patients were unable to pay for the cannabis they required for self-medication.

This situation has now been changed by the above law. In certain cases, medicinal cannabis products can now be prescribed to patients, with the costs borne by statutory health insurance. This applies to cases in which there are no other drugs available for the treatment of the disease or symptoms, and where a noticeably positive effect may be expected with regards to the course of the disease or severe symptoms. Patients will then receive a prescription from a physician, which they can redeem at a chemist. Apart from these new aspects, the refund possibilities for medicinal cannabis products already available before the law came into force have been extended; this relates to the finished medicinal products Sativex® and Canemes® as well as the magistral preparation Dronabinol.

The Federal Opium Agency of the BfArM had a substantial involvement in the development of the law. “With a view to patient supply, we expressly welcome that decisions on treatment with medicinal cannabis products are made solely by the attending physicians,” emphasises the Head of the Federal Opium Agency, Dr Peter Cremer-Schaeffer. “Every treatment with

prescription drugs requires a sustainable doctor-patient relationship. This applies to medicinal cannabis products as well as to any other drug.”

The prescription of the drugs set out in Annex III of the Narcotics Law is only permitted if, on the basis of their own considerations, the physician arrives at the conviction that the application is admissible and advisable in accordance with the accepted rules of medical science. Where, however, the intended purpose can also be achieved by different means, the application of medicinal cannabis products is not justified.

To gain further knowledge on the effects of cannabis as a medicinal product, the Federal Opium Agency will conduct a continuous accompanying survey on the application of medicinal cannabis products until 2022. “At present we



only have limited knowledge of the effectiveness and safety of the drug,” says Dr Cremer-Schaeffer. Whilst there are numerous publications dealing with “cannabis as medicine”, the volume of scientific data which is actually evaluable is too low. “For this reason, the law provides for anonymised treatment data to be forwarded to us by the prescribing physicians.” This is exclusively information that would be documented anyway within the scope of the anamnesis process or the course of the therapy. Additional examination or further surveying of the patients is not necessary. The patient data is anonymised and the identification of the forwarding physicians within the scope of the accompanying survey is impossible.

The forwarded data, for example on diagnosis, treatment, dosage and side effects, is evaluated by experts from the Federal Opium Agency. Among other things, the aim is to generate data in the areas of application and the patients’ age structure, as well as on the effectiveness and safety of the medicinal cannabis products when administered.

This is valuable information for the future use of medicinal cannabis products, explains Dr Cremer-Schaeffer. “Although the accompanying survey does not qualify as scientific research in terms of our requirements for autho-

risation studies, important findings can be expected, which may lay the foundations for future research.” The results are published and are thus available for all interested parties dealing with medicinal cannabis products from a scientific point of view.

Moreover, the accompanying study forms the basis for the Federal Joint Committee, enabling decisions on further refund of treatment costs for medicinal cannabis products.

The issue of “cannabis as medicine” is a major challenge for the BfArM, says Dr Cremer-Schaeffer: “We at the Federal Opium Agency have been facing this challenge for over ten years now, to an ever-increasing extent.” One of the main areas of focus has also been to ensure a supply to patients of pharmaceutical grade cannabis. “We use our experience and expertise to expand our knowledge of cannabis as a therapeutic drug and to drive forward the development of such drugs,” says the Head of the Federal Opium Agency. “Our paramount aim in this context will continue to be ensuring a supply of appropriately approved finished medicinal products for patients.”

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We use our experience and expertise to expand our knowledge of cannabis as a therapeutic drug and to drive forward the development of such drugs. Our paramount aim in this context will continue to be ensuring the patient supply of appropriately approved finished medicinal products.

DR PETER CREMER-SCHAEFFER



# Homeopathy: The BfArM has its eye on users' safety

When German pharmaceutical law was reformed in 1976, lawmakers expressly professed themselves to a “scientific pluralism in drug therapy”, which would need to be “clearly reflected” in the field of the authorisation of medicinal products.

The requirements for proof of concept for medicinal products from special therapies, including homeopathy, are influenced by this objective.

Today, the German Medicinal Products Act (AMG) expressly envisages consideration of specific aspects in this context. In accordance with this, there are special rules relating to proof of concept and market access for these products.

Thus, applications can be made for homeopathic medicinal products for authorisation according to Section 21 ff. of the German Medicinal Products Act or for registration according to Section 38 f. of the German Medicinal Products Act. The product can only be brought onto the market after the successful completion of one of these procedures.

Registered homeopathic medicinal products can thereby be introduced without indications. Accordingly, the legislature does not require a proof of concept for this group of medicinal products. By contrast, homeopathic medicinal products which specify areas of application (for example “for feverish respiratory infections”) may only be introduced with authorisation from higher federal authorities.

“Naturally, all homeopathic medicinal products – like every other medicinal product – are fully assessed by the BfArM during their application procedures,” explains Dr Christiane Kirchner. Together with Dr Christine von der Heide, she leads the specialist area of “Homeopathic and anthroposophical medicinal products” in the form of a so-called tandem model. The BfArM is certified as a family-friendly employer and focuses on offering these kinds of job-sharing positions. The responsibility for performing professional tasks and leading a team is thereby taken on by two people. This way, management, among other tasks, is possible on a part-time basis. The tandem model offers the chance to bring different competencies and experience into management tasks and optimally complement each other, according to Dr Kirchner. “Our cooperation is characterised by close teamwork, a high level of communication and mutual trust. Our primary objective is to guarantee the safety of medicinal products, and thereby patient safety,” emphasises the pharmacist, who has been working in the field of special therapies for 27 years. “That’s why these medical products are tested for their quality and safety in the course of both authorisation and registration procedures.”



This also includes a detailed toxicology test. The purpose of this test is to prove that the homeopathic medicinal product is harmless under the specified conditions of use. “We also take into account the toxicological risk for certain groups of people, such as children and pregnant or breastfeeding women, if the medical product is intended to be approved or registered for use by these groups of people,” says Dr Kirchner. The BfArM checks the documentation of the pharmaceutical company and also carries out its own research and calculations.

When a homeopathic product for teething problems in small children led to rare lethal side-effects in the USA in 2016, the Federal Institute was therefore immediately able to give the all-clear for Germany. In the USA, the teething products contained too high a percentage of an active ingredient stemming from belladonna, which led to the side-effects. The American health authority, the FDA, does not monitor these products for harmlessness, resulting in these fatal consequences. “Here, our situation is very different,” explains Dr Christina von der Heidt, who has been working for the BfArM in the field of homeopathic medical products for six years. “In Germany, the Medicinal Products Act ensures that homeopathic medical products are continually and systematically monitored, even after they have been introduced.” The marketing authorisation holders are subject to the same pharmacovigilance obligations as for other medical products. “And we have the same options for implementing measures for the protection of patients – up to the withdrawal of authorisation or registration.”

Hence, there are differences just in the proof of concept for homeopathic medical products. “The Medicinal Products Act specifies that not only scientific data, but also the

#### Division 4: “Special therapies and traditional medicine”

Division 4 of the BfArM is responsible for the scientific evaluation of medicinal products from the fields of special therapies as well as traditional medicine.

Its field of activity includes not only the preparation of professional statements on pharmaceuticals and medicine, but also the accompaniment of the entire project up until decision processing in the area of authorisation or registration.

Through their participation in national and international committees, the scientists play a decisive role in converting current scientific knowledge into EU and WHO guidelines.

medical experience of the relevant therapeutic facilities should be taken into account,” says the biologist. “With a view to the treatment of serious illnesses, however, there are clear limits.” Depending on which area of application the product is intended for use in, the data must fulfil the appropriate requirements. “We always have an eye on the safety of the product and the application”, emphasises Dr von der Heidt. This is particularly true for the treatment of serious illnesses. “Here, a study is a prerequisite for authorisation.” So far, however, the BfArM has not approved any homeopathic medical products where the applicant has referred to a suitable study to prove the product’s effectiveness.

# Dementia: development of new diagnostic approaches

The number of dementia patients in Germany is expected to rise to nearly 2.6 million in 2050. The socio-economic consequences of this development require new diagnostic and therapeutic measures in the field of dementia treatment.

To support the often unsuccessful past approaches in the research and development of innovative anti-dementia drugs, the “Experimental Neuropsychopharmacology” workgroup at the BfArM is working on the development of new diagnostic approaches in the field of dementia treatment, among other things, in order to be able to confront the tremendous socio-economic impacts.

Our understanding of the complex pathogenesis of Alzheimer dementia has been strongly supported by basic in vitro research and pre-clinical animal in vivo studies. However, the vast number of phase III studies with a negative outcome over the last 15 years and the associated limited predictability make it clear that crucial aspects of understanding how Alzheimer dementia works are still lacking.

Apart from cognitive and behavioural biology approaches, biochemical analysis methods and functional imaging in particular play a central role in diagnosis and progression monitoring today. For a long time, these procedures side-lined clinical electrophysiological methods such as electroencephalography (EEG). Only in recent years has it become apparent that in particular in vitro and in

vivo electrophysiology could have the power to revolutionise the prediction, early detection and progression monitoring of Alzheimer dementia. For some mental disorders such as schizophrenia, this has already been partly implemented. The translational character of Alzheimer-specific EEG phenomena gives grounds for optimism for dementia patients in future.

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First results underline the importance of complex EEG analysis in the characterisation of EEG fingerprints/ biomarkers in Alzheimer dementia.

PD DR DR MARCO WEIERGRÄBER

The “Experimental Neuropsychopharmacology” workgroup at the BfArM led by PD Dr Dr Marco Weiergräber pursues the in vivo EEG characterisation of selected Alzheimer mouse models, among other things. The project is being carried out in cooperation with the German Centre for Neurodegenerative Diseases (DZNE). “First results underline the importance of complex EEG analysis in the characterisation of EEG fingerprints/ biomarkers in Alzheimer dementia,” states Dr

Weiergräber. It has been impressively demonstrated that changes in specific EEG frequency ranges may become visible when the laboratory animals are still completely normal from a cognitive, behavioural biological and histological/structural point of view. This means that the in vivo electrophysiology in the animal model is already able to show the functional impacts of an increase of soluble

amyloid in the brain at an extremely early stage. “The analyses conducted by the BfArM, however, also emphasise how important it is to take into account the time of day, activity level and gender in the animal model. This makes corresponding sub-group analyses absolutely essential in order to be able to transfer the findings to the situation in humans at a later point,” points out the head of the workgroup.

In cooperation with the joint BfArM-DZNE “Pharmacoepidemiology” workgroup led by Prof. Dr Britta Hänisch, the scientists are also investigating the role of the LXR modulators from the Prazol group (proton pump inhibitors) in the formation and progression of Alzheimer dementia. Animal experiments and pharmacoepidemiological studies on glitazones have indicated for some time now that so-called PPAR and LXR modulators are able to modulate the course of Alzheimer dementia. In this context, the results gained in pharmacoepidemiological studies are coupled with the corresponding animal experiments to help understand the possibly underlying mechanisms. The main focus of the project is to investigate the impacts of long-term administration of proton pump inhibitors (Prazol substance group) on the cognition-associated theta and gamma frequency ranges in Alzheimer mouse models.

Epigenetic diet-related changes to brain waves and impacts on cognition: In an aging society it is important to train cognitive abilities even at an advanced age. It is also a known fact that nutrition plays a central role in cognition. However, little is yet known about how the nutritional habits of parents influence the cognitive abilities of their offspring. Within the scope of a cooperative project of the “Experimental Neuropsychopharmacology” workgroup of the BfArM, under the leadership of the DZNE “Molecular and Cellular Cognition” workgroup led by PD Dr Dan



Ehninger, it has been demonstrated that a methyl-rich diet in male mice results in a limited cognitive performance of offspring in the first generation. This phenomenon has been established both in vitro and in vivo.

Outlook: Besides genetic factors, epigenetic aspects play a central role in limited cognitive abilities within the scope of dementia diseases. The BfArM is currently carrying out research in the area of in vivo electrophysiology and the associated complex mathematical analyses, which ultimately are intended to define and validate EEG fingerprints/EEG biomarkers. The aim of the BfArM “Experimental Neuropsychopharmacology” is an improved visualisation of dementia progression and the definition of predictive markers for mild cognitive impairment (MCI) and manifested Alzheimer dementia. The BfArM is thus supporting the development of innovative anti-dementia drugs.

# Targeted support for young talent

Young scientific recruits have the opportunity to write their dissertations or implement research projects at the BfArM. Here too, the focus is on topics aimed at improving drug safety and thereby enhancing patient safety, as shown by the examples.

ANNA MARIA PAUL

## Structural neuroimaging of exposure to caffeine, paraxanthine and the role of CYP1A2 in caffeine consumers

Worldwide, caffeine is the most widely consumed psychoactive substance, and individual differences within the population with regards to tolerance and effects in the brain are often described in the literature. In our study, we attempted to visualise the effects of caffeine and paraxanthine, its main metabolite, in healthy consumers of caffeine, using structural magnetic resonance tomography. We

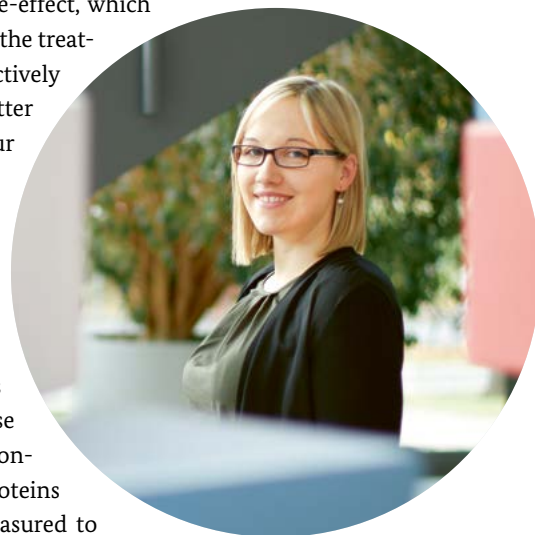
found associations between caffeine levels and alterations of the structural imaging signal in regions of the brain which showed a high receptor density for caffeine. On the basis of our data, structural MRT appears to be appropriate for measuring and presenting individual pharmacodynamic impacts of the receptor-mediated effect of caffeine.



VIVIEN HICHERT

## Predictive blood plasma biomarkers for EGFR inhibitor-induced skin rash

Cancer patients who are being treated with drugs from the group of so-called EGFR inhibitors often develop a severe acne-like rash as a side-effect, which is, however, a sign that the treatment is working effectively and is linked to a better prognosis. Through our research, we have discovered that a certain protein (hepatocyte growth factor, HGF) is present at a lower average concentration in the blood of patients with this rash than those without it. The blood concentration of such proteins could in future be measured to help predict the effectiveness of the treatment and in order to be able to treat the painful rash earlier or even to prevent it arising at all, whilst still obtaining valuable information on the further course of cancer treatment. This allows us to contribute to improved treatment safety.





DR KATJA SUSANNE JUST

### Drug-related falls in elderly people and the significance of pharmacogenetics

In the course of my specialist training at the BfArM to become a clinical pharmacologist, I work on research questions related to pharmacogenetics of elderly people, i.e. above 65 years old. It is unclear how

relevant pharmacogenetic particularities are in older people. For the elderly, drug therapy often leads to unwanted side-effects, such as dizziness, loss of consciousness or loss of balance. This can result in falls, which can have serious consequences for older people. It is thereby conceivable that, for example, decelerated or accelerated metabolization of drugs leads to falls in the elderly.

For example, genetic variations of drug metabolising enzymes are known, which could influence the dosage required. Our target is to understand if pharmacogenetic polymorphism has an effect on drug-related falls in elderly people, and if so what that effect is.



DR MATTHIAS VOGEL

### StemCellFactory III – Investigation of central nervous system-specific drug metabolism, using iPS cell-based cortical organoids (AP3 and AP4)

Drugs can be broken down not only in the liver but also in other physiological compartments by the cytochrome P450 (CYP) enzyme. There are clear differences between the CYP enzyme composition of the liver and that of the brain.

In a collaborative project between the BfArM and the University Hospital of Bonn, blood donations from patients are used to obtain neuronal organoids via induced pluripotent stem cell technology. Subsequently, studies of the CYP genetic expression and detection of CYP metabolites using high-performance liquid chromatography tandem mass spectrometry are carried out at the BfArM. On the basis of active substances, the results can be used to predict specific degradation processes in the central nervous system, which would not be apparent from blood plasma profiles alone. New questions of whether hitherto unknown toxic metabolites occur locally or to what extent substances accessible by the central nervous system are broken down independently from the liver serve as the basis of further research projects within drug treatment safety and individual pharmacotherapy.



# Analysis of suspected UARs: how to identify risks even better

In the “EudraVigilance” database, reports on suspected unexpected adverse reactions (UAR) from throughout Europe are processed and stored. These reports are investigated at the BfArM by an internal research group.

In the research groups, scientists are developing further methods in order to be able to analyse and exploit such reports even more efficiently.

The so-called spontaneous reporting system is an established and important surveillance instrument for medicinal products. It is based on reports on suspected unexpected adverse reactions made by physicians and other health care professionals as well as by patients. These reports are pooled and stored in the European EudraVigilance database. The reports are crucial for identifying drug risks as quickly as possible. To achieve this, the authorities depend on well-documented reports on UARs which are observed during daily practical use of the drugs. From the many reported symptoms, they then filter out those that may be the first sign of a previously unknown adverse reaction or discover that a known adverse reaction is suddenly being reported much more frequently.

The knowledge on the safety of drugs is not complete when initial approval is granted. Mainly, this is because the clinical testing of a drug is performed on a relatively small number of selected patients. Rare or very rare adverse reactions, interactions or other risks associated with the use of the drug usually cannot be detected in clinic testing prior to authorisation.

The Medicinal Products Act of the Federal Republic of Germany therefore provides for continuous and systematic collection and evaluation of experiences gained on the product's use once it has been authorised.

To further improve the evaluation of this data, a special focus is placed on the analysis of the suspected UARs. The

BfArM has its own research project, headed by Prof. Dr Bernhard Sachs, which aims to further optimise research options relating to the UAR database. The allergist and dermatologist has been employed by the federal institute for 16 years. A joint research project with the Institute of Medical Biometry, Informatics and Epidemiology (IMBIE) of the University Hospital Bonn endeavours to further optimise analysis options for UAR reports and to ensure even better identification of risk factors for the development of UARs. Prof. Sachs aspires to create direct benefit for both physicians and patients.

**Prof. Sachs, spontaneous reports, or in other words reported suspected UARs, for instance submitted by general practitioners, are the focus of the project. Why is it so important to carry out research on these UARs? What goals are linked to the project?**

UARs can be of great importance for patients and their attending physicians. For instance, they may cause a necessary treatment to be abandoned. Our aim is to develop, implement and establish innovative methods for the analysis of reports in UAR databases.

These new procedures should make it possible to filter out drug risks from the data even more reliably. The overarching goal is to protect patients even better and inform physicians even more accurately on specific UARs. This way, analyses in UAR databases may play an even bigger role in further increasing drug therapy safety.

**Specifically, how is the project being implemented by the research group?**

To begin with, we conducted an overall general analysis of the UAR reports in the database, or in other words an inventory of our national UAR database. Among other things, we determined how many reports are recorded in total, which drugs are most frequently subject to suspected UARs and what adverse reactions they most commonly trigger. In addition, we investigated where the reports of physicians and patients differ with regard to drugs suspected of UAR and the adverse reactions. Based on this, search algorithms will be developed for computer-aided database queries. The results will then be analysed, both from a biostatistical and a medical perspective. In doing so, the main focus will be on abnormalities – such as an accumulation of an adverse reaction when a drug is used intravenously.

**How is such a research project of special significance for the regulatory activities of the BfArM?**

The regulatory Pharmacovigilance division of the BfArM is also involved in the research project. This is intended to ensure that the research results are actually implementable. It is our aim that the newly gained findings from the research project are made directly available for physicians, pharmacists and patients. For example, in the form of a “Dear Doctor Letter”, an amended summary of product characteristics for the physician or the package leaflet (for the patient).

**What impact does the work on this project have for the research at the BfArM?**

The BfArM does not conduct basic research but research that is directly related to its official tasks. Ensuring and improving the safety of drugs is a key responsibility of the BfArM, and for this reason, the analysis of reports on adverse reactions plays a special role.



Accordingly, the research projects of the BfArM concentrate especially on the investigation of patient-side factors which potentially constitute increased personal risk of developing an adverse reaction when using a certain drug. The method used in these investigations can, for instance, be laboratory testing methods or UAR reports, as is the case here. Our research project works with this pharmacoepidemiologic approach, which is also the preferred method of choice in the research fields investigated by the BfArM.

# Biostatistics: The BfArM is researching more efficient therapies

Treatment concepts and drugs which are matched to the patient's individual genetic pre-disposition – these are the medical therapies of the future. At the BfArM too, research is being carried out in the fields of pharmacogenomics and individualised medicine.

In the biostatistics research group, experts are developing methods to better evaluate and understand risks and benefits in patient groups with differing genetic pre-dispositions.

Before a drug receives approval, it is tested in extensive studies. Among other things, its risk-benefit ratio is examined. This gives information on whether the positive therapeutic effect of the drug is suitably proportional to the potential risks of the treatment. However, the potential benefit and risks may not be identical for each patient, since how a person responds to treatment is also dependent on their genetic pre-disposition. This dependency is being investigated at the BfArM by the research focus on pharmacogenomics and individualised medicine. The research

group, led by Prof. Dr Julia Stingl, addresses individual differences in the effects of treatment which are produced by such genetic differences. Their goal is to better recognise risks and to be able to individually adjust treatments.

For this process, biostatistics plays a special role, in which efficient methods of biomarker identification are developed and investigated. The head of the biostatistics research group is Dr Norbert Benda. He describes the important contribution made by the BfArM here towards increasing the effectiveness and safety of medicinal products. According to him, advances in genetic research and DNA sequencing in particular give cause for hope that certain features or genes can be used to specify patients where a large benefit or a low risk can be expected from a therapy. "Ultimately, this method should save patients from unnecessary therapeutic attempts. Reliable determination of such patient groups, however, is significantly more complex than is popularly believed," says Dr Benda.

Safe determination of these patient groups continues to set special challenges for research. "A limited number of patients in clinical trials are faced with a multitude of options for defining these patient groups," says the leader of the research group. "This means that random results are likely." In order to differentiate patients who benefit more from a particular therapy from others, however, a large number of people must take part in the relevant studies. But studies of this size, explains the expert, are unrealistic. "In this respect, it is extremely important to develop a good and valid methodology in order to be able to safely



define these differentiations. This is what we are working on at the BfArM.” For this purpose, the Federal Institute has initiated a joint project with the University Medical Center Göttingen (Prof. Dr Tim Friede and Prof. Dr Jürgen Brockmöller). In this project, statistical methods for the identification of patient groups are developed and investigated in extensive simulation studies. In addition, possibilities for using various data sources from clinical development programs are explored, in order to make reliable statements on personalisation. During this process, new models for sub-group identification from several possibly different studies are developed. Here, the scientists can refer to the so-called Bayesian approach, where the heterogeneity between the studies is modelled by previously accepted distributions, in order to obtain robust results.

“Alongside the development of innovative methods for personalisation, we also need to better understand our limits,” says Dr Benda. “These result from the fact that we unfortunately often do not have enough data for the relevant efficacy parameters and that treatments for the same patients usually cannot be compared with each other.” In this respect, it is important to understand on the one hand the assumptions on which the development of per-

sonalised medicine is built, as well as to develop new, highly selective statistical methods which are based on plausible assumptions, according to the expert.

Furthermore, since 2017 the BfArM has been a project partner of the large European research association “HARMONY”. Here, a large number of European research institutes are working on standardised generation and reliable evaluation of large clinical databanks on the treatment of haematological cancers. For this project too, the focus is on more precise evaluation of treatment options. In future, patients suffering from leukaemia and other haematological cancers should benefit from more efficient treatment.

“The identification of biomarkers and a sound methodology for this will continue to increase in importance for targeted patient care in future,” stresses Dr Benda. “We are well-prepared for this development and can rely on both our employees’ expertise and our broad networking.”

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The identification of biomarkers will continue to increase in importance for targeted patient care in future. We are well-prepared for this development and can rely on both our employees’ expertise and our broad networking.

DR NORBERT BENDA



# Developing new methods to improve medical device safety

**Big Data:** Increasing quantities of data offer the BfArM the opportunity to quickly gaining more insights on medical device risks in the future. Dr Robin Seidel, from the specialist area of “Methodology research and medical device safety” talks about new forms of risk identification.

The number of medical device incident reports received by the BfArM per year has approximately tripled in the past ten years. In 2017, almost 14,000 reports were received, and this number continues to grow. The BfArM uses this valuable information to improve safety in the use of medical devices, whereby Dr Robin Seidel’s team develops new methods for the risk-related assessment of large quantities of data. In the future, this will allow scientists working in regulation to gain new insights into risk signals more quickly and more precisely.

**What opportunities do the new possibilities for risk identification offer for the work of the BfArM – and thereby also for patient safety?**

Risk evaluation of medical devices on the basis of incident reports is one of the main pillars in the field of medical device safety. The work of our assessors targets quick recognition of risks and clear recommendations, on the basis of which other players, such as manufacturers and regional authorities, can swiftly get effective measures towards patient protection off the ground. In order to be able to achieve this even when report numbers continue to grow in the future, our specialists need new tools to support their work. Ultimately, it is a matter of recognising as quickly and reliably as possible after a report has been filed what risks are involved and what measures are required for further clarification and, if necessary, risk minimisation.

**Does this ultimately mean that more insight is gained from the same data?**

Our aim is to develop approaches on several levels, in order to be able to use our data more intensively to support scien-

tists. Alongside analyses of the manufacturers’ reporting behaviour, e.g. compliance with reporting deadlines, we can also gain insight into whether there are differences between different manufacturers within a product group, e.g. how intensively various manufacturers identify causes of error. In the future, we would like to be able to better recognise cross-product risks, e.g. problems with certain materials or frequently used components such as batteries, in order to be able to better process them for the assessors. One of the major challenges of this is that risk reports for medical devices are mainly written in free text, which is unstructured from a data point of view. We therefore need to be able to process information as automatically as possible, while making sure it is reliable for further recognition of risks.

**What does this mean specifically? How are you approaching the challenges?**

As our research, e.g. on appropriate analysis algorithms and visualisation options, is directly linked to regulatory practice, it proceeds above all on the basis of the real data which our colleagues work with on a daily basis. However, this also means that they do a large amount of preparatory work, categorising result reports by keywords such as “Health effect”, “Device problem” or “Evaluation result”. This significant time investment creates the basis we need to test different pattern recognition approaches for quality, i.e. to compare with the experts’ assessment. This enables, for example, automatic categorisation of incidents, either based on specific ontologies or by means of similarity and distance measures, or alternatively based on simple clustering of thematically similar reports. From this basis, we are able to develop analysis algorithms and use suc-



cessive IT systems in our work. This cannot be achieved overnight – but based on early results, we can already see that we are on the right track to be able to recognise patterns more quickly from the data available. We can already recognise and visualise similar reports or risk-related patterns quickly on an experimental level using text-mining procedures. In the future, we aim to generate overviews from this, which can be quickly adjusted to answer relevant questions: What is reporting behaviour currently like for a particular medical device, what do error patterns look like for a particular product group, how effective is a corrective measure, could a cross-vendor problem exist? To this end, we will also integrate classification methods from other fields, for example artificial neural networks.

**Is the BfArM also initiating new solutions on an international level with this approach?**

With our approach we are treading new ground for Europe in the field of IT-supported risk assessment of medical devices. For this reason, we work in close collaboration with the other European authorities for medical devices in order to bring about the necessary requirements and alignments. For example, this includes creating structures which allow detection of signals without having to first transfer unstructured data into a structured form, on a European level as well as a worldwide level via the International Medical Device Regulators Forum. From this, we hope to gain enormous advantages for rapid worldwide communication with other authorities regarding product risks.

**Specifically, how can risk evaluation assessors profit from your research?**

It is important to us that our research results and IT solutions tangibly and noticeably – ideally, measurably – support our assessors in their daily work. Ultimately, our aim for the future is to process incoming risk reports as automatically

as possible and present the results in a helpful, e.g. graphical, format. Among other things, the advantage for evaluation will be that we are able to individually visualise risk profiles and correlations, creating a more comprehensive overview and a better understanding in a short time. The focus thereby will at all times be on the scientists' assessments, which will always be the deciding factor. As researchers, however, we aim to support them as much as possible, enabling them to continue to make sound and reliable decisions, even against a background of constantly rising numbers of reports and increasing quantities and complexity of information.

**Between research and practical risk minimisation – is this a typical job description for you in a medical device authority?**

At first glance, certainly not. At the BfArM, however, the use and also the creation of new methodological approaches and IT tools is a highly topical subject in all fields. It is only logical that I, as a biologist/biomaterial scientist and developer, have interesting creative possibilities in my function as a project leader, for example when it comes to new solutions for ontology-based software to support risk evaluation. In this respect, with the establishment of the new specialist area “Methodology research and medical device safety” in the medical device department, the BfArM has not only given the green light to the development of new forms of identification of medical device risks, but has also created entirely new career prospects directly linked to regulatory practice for specialists at the interface between programming and the natural sciences.

# Anaesthesiology equipment: investigating operating errors

Risk assessment of medicinal products targets the elimination of systematic product defects. But even beyond that, the BfArM contributes to safe use of medical devices thanks to its dedicated experts. Dr Andrea Brinker and PD Dr Kathrin Lange discuss risk minimisation in intensive care.

Incident reports are an extremely important source of information for the BfArM. They allow the BfArM to assess risks and give concrete recommendations for risk minimisation to manufacturers, users and the monitoring authorities of the federal state. However, there is often no systematic product defect, despite suspected cases being reported. Nevertheless, there are risks in connection with medical devices which must be addressed. For example, in the operating theatre and intensive care: Dr Andrea Brinker, anaesthesiology specialist from the field of “Active medical devices and in vitro diagnostics” and PD Dr Kathrin Lange, head of the specialist area “Methods research and medical device safety” and a psychologist with a focus on attention and perception, in close collaboration with clinics, are committed to reducing risks in the operation of various models of anaesthesiology and intensive care equipment.

## **Dr Brinker, what risks are shown by the incident reports you receive and audit regarding anaesthesiology and intensive care equipment?**

For example, we frequently see that operating anaesthesiology and intensive care equipment can lead to serious problems. This can be due to a systematic product defect of specific devices. In these cases, we can give the manufacturer a product-specific recommendation. However, usage risks can have different causes – even causes which have nothing to do with an individual product directly. For instance, this is the case when different models of equipment are used in a clinic for the same function. In one case, we were told that it was not possible to ventilate a patient with a particular ventilator. The ventilation pressure was below the

value configured by the user. The reason for this was that the chosen ventilation pressure was limited by the equipment’s pre-configured alarm limit. The user was used to equipment which does not allow a ventilation setting which would later be limited by the alarm settings to be chosen at the input stage.

## **So a risk to patients can also arise from specific configurations of medical devices?**

### **Dr Andrea Brinker:**

Whether a medical device can be used safely is always dependent on the interaction between product, usage context and user. If there is no systematic product defect, we cannot in the proper sense make a recommendation for action to the manufacturer. Of course, we cannot leave it at that and see a need for action in line with preventative health protection.



**PD Dr Kathrin Lange:**

In the case described above, it appeared that the use of different ventilation devices in the clinic concerned was contributing to operating errors. When we take into account how the processes of memory, attention allocation and action control work, this type of influence is to be expected, from a cognitive psychology perspective. Among other things, the practical question arose of whether the presence of different models of equipment is the exception or the rule, and in what way these models differ.

**Dr Lange, how did you proceed in order to win further knowledge from practice?**

Together with clinics, we established how typical such situations are for daily clinical practice. In the course of a questionnaire-based survey of medical technicians in German clinics with intensive care units, we asked how many different models of the same group of equipment are used there. Furthermore, we asked the medical staff of the clinic for anaesthesiology at a university hospital what their experiences of using different models of equipment have been.

**What was the outcome, Dr Lange?**

In many clinics, different models of ventilators, syringe pumps and patient monitors are used in parallel, often including equipment from different manufacturers. Almost all users have already worked with a variety of models of equipment. Many of them reported errors or uncertainty when using equipment, which they ascribed to experiences with different equipment. Our surveying of medical technicians and users suggests that there is significant potential for this type of operating error.

The work of Dr Andrea Brinker and PD Dr Kathrin Lange reflects the BfArM's aspirations, as well as the wide range of tasks and creative opportunities available to its team of experts to improve patient safety.

**Dr Andrea Brinker:** "My practical experience as an anaesthesiology specialist profoundly helps me to keep all the facets in mind of this complex interaction between technology, the regulatory framework and the clinics' use contexts. I continue to work in the operating theatre regularly to retain my practical view. This provides advantages for the authorities, clinics and patients."

**PD Dr Kathrin Lange:** "As a qualified psychologist, I have researched and taught in the fields of attention, perception and memory. Alongside technical and medical aspects, the question of how people absorb information and use it to steer their behaviour is an important factor in judging operating errors appropriately and recognising the system behind them. When it comes to the BfArM's research work, the close link to the practical application for patient safety has a particular appeal for me."

**How can risks arising from equipment diversity be minimised in the future, Dr Brinker?**

There is no easy answer to that. We are currently discussing optimisation options for standardising equipment via the relevant guidelines. Another possibility for risk reduction is standardising the equipment fleet within a clinic. However, there may also be reasons for the usage of different equipment models, meaning that each clinic must weigh the issue up carefully. Another important aspect are instruction briefings: these must take place for the equipment available and – this is extremely important – must be refreshed regularly, so that even equipment which is used infrequently can be operated with confidence. In this respect, we are not only active in risk assessment regarding this topic, but also in consultation with associations of medical experts and standardisation committees in order to set solutions in motion there.