Federal Institute
for Drugs
and Medical Devices

#bfarmDigitalFuture

Shaping health together:
The BfArM as a partner in Germany and Europe.

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Content

Dear reader,

"Only if we take advantage of the opportunities digitalisation offers us, can we make patient care better": As early as 2019, this sentence by Federal Health Minister Jens Spahn clearly outlined the course the development of the healthcare system has to take. Not least on account of the corona pandemic has digital-isation become increasingly important in this area. Once more, it has shown how essential it is for us in Europe to act together and to be able to access common data and networks for this purpose. A rapid merging of data, as is currently being done for Covid-19 research purposes, while taking into account semantic and technical interoperability, is only one example of many, but also one that shows how we are now stronger as the integrated "new BfArM". Digital health applications open up a wide range of possibilities to support the recognition and treatment of diseases and to help people on their way to a self-determined, health-promoting lifestyle.

From the very beginning, the Federal Institute for Drugs and Medical Devices (BfArM) has actively participated in this strategy set out by the Federal Government and the Ministry of Health. We associate very specific concepts and visions with the field of "digitalisation" that consistently pervade all areas of our work.

Commitment to the care of all patients, advancing new treatment options and making joint use of the advantages of digitalisation:

these are the core elements that determine our activities. Since 1994, the BfArM has been working to ensure the efficacy and safety of medicinal products not only in Germany but also throughout Europe. The field we are working in has always been characterised by highly dynamic processes. However, our mission has remained the same at all times: the primary goal of all our measures is to increase patient safety.

We are thus making use of the opportunities offered us by digitalisation in order to continue to perform our core tasks as best possible: the authorisation of medicines and the improvement of their safety, the risk assessment and evaluation of medical devices and the monitoring of the legal traffic in narcotic drugs and precursors, as well as the handling of large amounts of data with a view to interoperability and better care. In this report, we would like to present some of these areas and show how the Federal Institute is already helping to shape these developments of the future today and how it intends to continue to further advance them together with its cooperative partners.

Prof. Dr Karl Broich, President of the BfArM

Designing digitalisation together

Digitalisation is in the process of fundamentally altering the nature of healthcare provision. Above all, the rapidly increasing amount of health data offers enormous opportunities: "How we prepare care-related data from many different sources and combine it with the knowledge gained from clinical studies will crucially determine our work in the future," says Professor Karl Broich, MD, President of the Federal Institute for Drugs and Medical Devices (BfArM).

As the largest European drug regulatory authority, the BfArM has always been active in an environment that is particularly characterised by highly dynamic processes: scientific and technological innovations, exponentially increasing data volumes, Artificial Intelligence (AI) or novel designs of clinical studies are only some of the topics to which it reacts promptly and efficiently.

The BfArM is actively working on harnessing these developments in order to execute its core tasks and thus serve patient care as best possible. Digitalisation offers new possibilities for the development of therapies for efficient healthcare. "We will make use of the opportunities that are opening up," explains Professor Broich. "Innovations should reach patients without unnecessary delay."

With its worldwide leading digital competence, the BfArM joins forces with the other institutions in charge of the approval and surveillance of medicinal products and medical devices. Close cooperation with different players in the relevant networks is of utmost importance. Among others, the Federal Institute participates in the "Health Innovation Hub", a think tank for digitalisation in the healthcare system developed by the Federal Ministry of Health. Together we have elaborated the principles and requirements for Digital Health Applications (DiGA). There are also corresponding connections with the University Hospital in Bonn, where possibilities for the application of new technologies in medical care are being evaluated. Last but not least, the BfArM is active in the innovation project "Giga for Health", where an app for reporting medical device risks is being developed.

The focus is always on the intelligent use of the constantly growing amount of health data. "Big Data" is closely linked to the concept of "Real World Data", which originates from the "real world", i.e. from

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medical practices or health insurance companies, rather than from clinical studies. Data collected by patients themselves is also playing an increasingly important role, e.g. due to the use of medical apps that collect and evaluate health data.

One major challenge is that all this data is initially available in an unstructured form. It must therefore be prepared in such a manner that it can be processed and interpreted in the same way by different recipients and in different systems. This is the only way to ensure a smooth exchange of data. "Interoperability" [22] is the keyword here, and it is this interoperability that makes the effective use of data possible in the first place. Therefore, the BfArM places particular emphasis on this processing of data. For example, a separate executive department "Classification Systems" and a semantic centre are working on the development of corresponding systems. "We do not only focus on the national level," says Professor Broich. "Together with our colleagues from the EU, we are working to ensure that health data can be used across national borders, for example for research purposes."

Patient-oriented use of health data for Europe in combination with EU-wide cooperation was the theme of the conference "Digital Health 2020 – EU on the Move" in November 2020. There, the Commission and the German EU Presidency, represented by the German Federal Minister of Health Jens Spahn, exchanged views on the creation of a

secure European environment for health data. The BfArM is in close contact with the key players in this field and actively promotes this development on the European level. This applies, for example, to the "Task Force on Big Data" [26], which was established by a consortium of the national approval authorities and the European Medicines Agency. "We want to be a pioneer for Europe here and participate in the development of concepts which – while respecting data protection and information security – will enable the systematic consolidation and efficient use of this data in future," emphasises the BfArM President.

At the BfArM, the subject of digitalisation is associated with very specific ideas and visions that permeate almost all areas of the Federal Institute's work. AI [18], for example, is one of the key technologies of digitalisation and has been used successfully at the BfArM for many years. Here, an AI computer offers different sectors the possibility to analyse large amounts of data.

However, AI and "Big Data" are not only used with regard to medicinal products, but are also supposed to assist in the monitoring of medical devices [14]. For example, keywords entered by users in free texts can provide information on incidents involving medical devices. These keywords have to be identified and analysed – a typical task for AI – to quickly detect the important details in the overall picture. Last but not least, it will be made easier for users to digitally record and report problems with a medical device in the

future. In this way, data will also be generated, which will be evaluated accordingly at the BfArM.

"With regard to the detection and treatment of diseases, medical apps offer patients and physicians completely new possibilities," explains Professor Broich. "We also see great potential here and have accompanied this development from the very beginning."

From the start, the BfArM has been involved in shaping the digitalisation strategy of the Federal Government and the Ministry of Health. Since the Digital Healthcare Act (Digitale-Versorgung-Gesetz, DVG) came into force on 19 December 2019, such digital health applications (DiGA) can be prescribed by physicians and psychotherapists and are reimbursed by health insurance companies. The BfArM is responsible for the evaluation procedures of the applications, as well as for the list of digital apps that are classified as reimbursable health applications after successful testing. "We consider ourselves the developers' partners [10], working together with them to provide patients with the new technologies," says Professor Broich.

Aside from these opportunities, the BfArM as a regulatory authority always keeps an eye on the possible risks. Thus, the Institute also addresses questions on data protection, information security and data use. The use of data that users themselves collect via the apps is a particularly important issue

in this context. In the USA, not only the US Food and Drug Administration (FDA) but also corporations have recognised the value of such health data. "In Germany, we now have the chance to shape the digitalisation of the healthcare system in our favour and to promote our own independent solution," emphasises the BfArM President. The goal of the higher federal authority is thus clearly defined: "We will continue to be at the forefront of this development both in Germany and in Europe." The BfArM will always keep its core tasks in mind and do everything possible to ensure that patients have quick access to effective and safe innovations.

Professor Karl Broich also has a clear picture of the further development of healthcare: "I can well imagine that in the future we will be developing many more tailored therapies for patients – and this in an ecosystem of digital and classical medicinal products and medical devices in which the patients are the focus of our attention."

Professor Karl Broich, MD
MD specialised in Neurology and Psychotherapy, lecturer and supervisor for behavioural therapy. Has been working at the BfArM since 2000, first as head of the Neurology/Psychiatry Unit, then as head of Division 4 "Licensing". Since 2013, honorary professor at the Medical Faculty of the Rheinische Friedrich-Wilhelms-University, Bonn. From 2009 to 2014, Vice President, and since 2014, President of the BfArM.

New paths and a glimpse into the future

The development of medicinal products and medical devices is characterised to a significant extent by increasingly dynamic processes and a great potential for innovation. In addition to other aspects, digital products open up completely new possibilities, which need to be explored in the most comprehensive manner. The Innovation Office provides regulatory support to developers while looking ahead into the future of healthcare at the same time.

Science and technology in the healthcare sector have advanced tremendously in recent years. Products such as health apps are setting new trends and the healthcare market's network is becoming increasingly digital. Digitalisation, especially, is making development cycles shorter and shorter. Consequently, the Federal Institute for Drugs and Medical Devices (BfArM) is now also being approached by new players on the scene: start-ups, research institutions and developers of digital applications seeking to bring their products to market.

The BfArM is acutely aware of the potential of this development; one of its top priorities is to ensure that patients have access to promising new medicines and medical devices as quickly as possible. Innovations must not be allowed to fail for lack of regulatory experience. Start-ups or smaller research institutes do not tend to have the necessary experience with regulatory processes. Accordingly, they rarely have comprehensive knowledge as to the requirements that have to be fulfilled when licensing and marketing their products.

In order to meet precisely this group of stakeholders at eye level and in the best possible fashion, the BfArM already set up its Innovation Office in 2017. This broadened the BfArM's scientific and regulatory advice service to include orientational information and procedural guidance. Since then, the Innovation Office has established itself as an uncomplicated first point of contact for start-ups, researchers and developers who need assistance with the formal requirements of the health market. "For the developers, we are somewhat like pilots who accompany them on their route through the licensing process or towards implementation within the healthcare system," illustrates Dr Wiebke Löbker who heads the Innovation Office. "The special nature of this mission is that sometimes we too have no precise idea at the beginning where the journey will lead us in the end."

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> **"Our work in the Innovation Office is an exciting task for which it is particularly important to be able to evaluate and anticipate future trends."**

After all, new ideas often also require new implementing strategies, which is precisely where Dr Löbker joins forces with the applicants. "An exciting task for which it is particularly important to be able to evaluate and anticipate future trends," explains the head of the department. "We must therefore keep track of developments in the healthcare sector and have to assess applications bearing in mind these possible changes."

Such foresight is facilitated by the fact that the Innovation Office enters into an early exchange with developers of innovative approaches – instead of waiting for them to contact the BfArM with their questions. The Innovation Office's work is thus characterised above all by substantial exchange on all levels: in the beginning, there was a "roadshow" and Dr Löbker continues to be present at numerous events, meeting the Innovation Office's target groups and introducing the BfArM's services at trade fairs, conferences and symposia. "The dialogue with the people who, for example, present their idea for a new approach to care is very important to us. It allows us to assess and prepare ourselves for the developments we will be facing in the coming years."

This process called 'horizon scanning' involves the systematic monitoring of existing trends and the identification of new developments. For the BfArM with its special position in the highly dynamic field of healthcare, this is an important task while at the same time being an element leading to mind change. "The Innovation Office does not consider consulting to be a one-way street," emphasises Dr Löbker. "From the very beginning, we focused on a constructive dialogue for both parties and actively sought feedback. Such response is important to us and is directly reflected in our work."

One example of this is the guide to "The Fast-Track Process for Digital Health Applications (DiGA) according to Section 139e SGB V". In this publication, the BfArM summarises the legal specifications and requirements of the DiGA procedure together with a transparent presentation of the evaluation criteria it applies. "In order to ensure that the information was indeed prepared in an understandable way for our target groups, we released the first version of the guide for commenting," describes Dr Löbker. This approach was very well received, so Version 1.0 of the guide now incorporates a lot of positive feedback and suggestions.

On the European level, the Innovation Office is also in close contact with colleagues from other regulatory authorities in the "EU Innovation Network (EU-IN)" in order to exchange information on new developments and trends as early as possible. For example, an EU-wide project, funded by the European Commission and coordinated by the BfArM, is currently focusing on how to improve the exchange between licensing authorities and the academic research environment

with regard to regulatory aspects to support innovation-friendly developments in the long term.

For a regulatory authority, accompanying and actively shaping innovative processes also means taking new paths and permitting creative approaches – for the head of the Innovation Office, this is exactly the right strategy: "Already, slow and very bureaucratic processes are no longer up to date, and they will certainly not be so in the future either. We have a responsibility towards the patients who rely on us to make good and safe treatment options available quickly." The Innovation Office sees itself as a "full-service provider" in this context. At the BfArM, the licensing of medicinal products and the medical device division are under one roof. Experts can thus be contacted directly and asked for advice during consultations. "Basically, we provide solutions from one single source and also, for instance, bring together competent contacts from outside the BfArM as well," explains the head of the department. "This way, we can ensure that such developments proceed without unnecessary delays and in compliance with regulatory requirements – from a project idea up to the prescription by physicians and the safe implementation by patients."

With regard to the future of healthcare provision, Dr Wiebke Löbker sees great potential, especially in the field of medical apps: "Apps will allow a completely new type of medical care: they will make the interaction between physician and patient or between patients and their relatives easier and faster." Apps can revolutionise the prevention of diseases by providing

information at an early stage, e.g. based on continuous monitoring, if important parameters have changed. Via mobile phone – or other "smart devices" of the future – it will then be very easy and, above all, possible for anyone to call up the appropriate options for action immediately: starting with a reminder to take specific medication regularly or instructions on how to deal with (disease) symptoms more consciously up to direct interaction with the physician.

"I believe that in the future we will no longer see a separation between digital and traditional medicinal products and medical devices as we do today," the head of the Innovation Office is convinced. "The products will merge into sort of a construction kit from which very individual treatment options – digital or conventional – can be put together. We will be accompanying this process and will see to it that such innovations will be feasible and will arrive in the healthcare system as quickly as possible."

Wiebke Löbker, PhD
University studies of Pharmacy. From 2009 to 2011, research assistant at the Institute of Pharmacology and Toxicology at the Free University of Berlin. From 2011 to 2016, consultant and team coordinator in the Pharmaceuticals Department of the Federal Joint Committee, focusing on early benefit assessments. Has been working at the BfArM as head of the executive department "Innovation Office/Change Management" and personal assistant to the President since 2016.

Supporting innovations

The dynamic developments in the field of medical devices will continue to pose particular challenges for regulators in the future, as innovations in this area do not stop at boundaries of indication, sector or technology. The BfArM assumes an important role in this context: it supports these innovations while at the same time ensuring that safe medical devices are available in the healthcare system.

Helping to pave the way and at the same time setting crash barriers: this is how Dr Wolfgang Lauer describes the task of his division "Medical Devices" at the BfArM – especially in view of the changes brought about by digitalisation, which is gaining ever greater influence in this field. While the term "medical devices" was previously associated primarily with "classical" devices for diagnostic or therapeutic use, this market has been changing rapidly for some years now. Software applications for smartphones and tablets, so-called "apps", have become everyday companions both when working and during leisure time. Accordingly, they have also found their way into the health sector.

In order to make the border between wellness applications and medical devices clear, the BfArM already

provided an orientation guide on its website several years ago, which helps developers to find out whether their product falls within the scope of the Medical Devices Act. Since then, the requirements and tasks the BfArM has to meet have continued to grow steadily. "We are currently experiencing a fascinating wealth of new approaches and possibilities in digital medical devices for diagnostic and therapeutic purposes," explains Dr Lauer, who has been head of the BfArM's "Medical Devices" division since 2011. "In this context, we are observing a fundamental change in the health-care system, which has already led to many new legal regulations and thus significantly influences our work."

Current legislative initiatives include the "Digital Healthcare Act" (Digitale-Versorgung-Gesetz, DVG), which came into force in December 2019. Since then, around 73 million insured persons in the statutory health insurance system have been entitled to receive so-called digital health applications, which can be prescribed by physicians and psychotherapists and are reimbursed by health insurance companies: "app on prescription", as the Federal Ministry of Health calls this step. In order to allow patients speedy access to good and safe innovative apps, a new method of

"Good healthcare requires safe and innovative medical devices."

ce, novel designs of clinical trials: the healthcare system is experiencing increasingly rapid changes along with the corresponding challenges these bring. Regardless

> "We are observing a fundamental change in the healthcare system, which is significantly influencing our work; we too must continue to develop steadily."

reimbursement for manufacturers was created. The BfArM plays a key role in this process, as it reviews these products with regard to safety, functionality, interoperability, quality, data protection and data security. In addition, the manufacturer has to show that its app or web application contributes to the improvement of care. Germany is an international pioneer in this field and our European neighbours in particular are following this initiative with great interest.

"We established a corresponding evaluation procedure at the BfArM very quickly so that the first applications could be submitted and assessed by us only six months later," explains Dr Lauer. "The entire procedure is a crucial step towards being able to harness the innovative potential of digital applications for healthcare." Along with these tasks, the BfArM is also evolving into a new direction. So far, the Federal Institute has not been involved in the process of deciding on the reimbursement of medical devices, which falls under social law. This is a step that can be taken after a medical device has been placed on the market and is independent of it.

Of course, classical medical devices such as artificial hip joints, heart valves or X-ray equipment will continue to be needed in the future to detect diseases, relieve suffering and tip the balance between life and death in emergency situations. "The example of digital applications shows, however, that we are at the beginning of a fundamental change in the way we deal with health issues," says Dr Lauer. In the future, patients will be able to exchange current information on their

personal health with their doctors and these in turn will be able to communicate individual diagnostic and therapeutic advice. Increasingly, networked services will be used, in which a variety of sensors will be connected with medical device functions, communication and individually tailored medical services.

This shows the broad scope and the crucial role that regulatory authorities will be playing here in the future. The BfArM's task in this context is not only to check the safety of the application for patients, it is also closely involved in processes that ensure significant – and secure – networking of data based on semantic and technical interoperability [22]. "In order to act in the patients' best interest, it is also important to provide new technologies in the first place," explains Dr Lauer. "Good healthcare requires safe and innovative medical devices and we clearly see ourselves as partners of the developers in this endeavour," emphasises Dr Lauer. "We are at their side from the very beginning with numerous offers of support to ensure that their ideas do not fail because of regulatory hurdles. At the same time, we are also constantly expanding our knowledge in order to adequately answer the new questions that arise when assessing such applications."

Dr Lauer also sees a clear trend towards the use of AI in the future evaluation of medical devices by the BfArM. This is because the amount and complexity of information on products and risks is steadily increasing, not least due to the use of digital applications, such as apps, as well as the short innovation cycles

in the medical device sector. In view of such large amounts of data, new possibilities for risk signal recognition and assessment are inevitably associated with the use of intelligent IT tools. "Our experts are supposed to be able to apply their specialist knowledge specifically to the evaluation of signals, instead of to the search for them," explains Dr Lauer. In the future, we will be applying automated analysis tools using AI, for example to search free texts for risk signals that allow conclusions to be drawn regarding the problem with the product. The particular challenge here lies, among other things, in the development of algorithms that allow risk-related information within free texts to be converted into structured data and analysed with regard to risk patterns. "In order to continue to be able to assess risks quickly and reliably in the future, our research group on medical device safety is developing new approaches for data-supported risk signal detection and for better consideration of human factors in the application of digital medical devices, which we also apply directly in our regulatory risk assessment," says Dr Lauer.

Patient safety should therefore also already be steered into new directions as early as when risks are being reported. For example, within the framework of a research project funded by the Federal Ministry of Health, the BfArM is currently investigating which aspects influence the reporting of incidents by professional users in order to derive measures for improved support of such reporting and to establish them in practice.

Within the framework of the "5G.NRW" innovation competition, a corresponding partial project of the BfArM is also supported by the Ministry for Economic Affairs, Innovation, Digitisation and Energy of the Land of North Rhine-Westphalia. In the future, it will supposedly be possible to report medical device risks to the authorities quickly and securely via an app, regardless of location. These reports will also be used as a basis for an improved risk assessment and for the even faster implementation of effective safety measures in cooperation with manufacturers and authorities of the "Länder".

Dr Wolfgang Lauer believes that the BfArM is well prepared for these developments: "Here at the BfArM, we have been dealing with all these topics thoroughly for years. We are in close dialogue, e.g. with universities and start-ups, providing information and advice on digital medical devices, giving important impulses for political decisions – together we are working to ensure that patients can continue to rely on safe medical devices in the future."

Wolfgang Lauer, PhD
Diploma studies in Mechanical Engineering and doctorate in Surgical Robotics. From 2008 to 2011, chief engineer and head of the research team "Risk Management and Ergonomics/Usability of Medical Devices" at the RWTH Aachen University. Has been working at the BfArM as head of Division 9 "Medical Devices" since 2011. Since 2019, Co-Chair of the European "Competent Authorities for Medical Devices" (CAMD) Executive Group.

Recognising the pattern within chaos

The future of medicine and its progress are inseparably linked to the evaluation of a wide range of health-related data and the use of Artificial Intelligence (AI). At the BfArM, AI is already being applied in specific fields. The Federal Institute aims to play a pioneering role for Europe in the use of these methods.

What influence do the genes of a human being have on the effectiveness of their medication? How can we find the optimal therapy for each patient? In order to answer such questions, medical research needs one thing above all else: data. Such data can derive from a wide range of sources, such as genome databases, from health insurance policies, adverse drug reaction reports and incident reports on medical devices, as well as from digital health applications such as medical apps.

The BfArM has long recognised the potential of "Big Data" for its work. In its scientific laboratories, for example in pharmacological and genetic experiments, the BfArM generates some of this data itself in order to find answers to regulatory and scientific questions. The data is then analysed and evaluated statistically, e.g. by searching for certain patterns or testing for associations between characteristic values of interest. Since 2019, an AI computer has been supporting the scientific staff of the BfArM's Research Department, enabling them to implement and execute innovative and computationally intensive data analysis procedures. Among others, these include methods of "machine learning", which is a subset of AI. Such methods always play an important role when finding or analysing complex relationships in high-dimensional and very large data sets.

Dr Michael Steffens is a member of the BfArM's Pharmacogenomics Research Group and deals, among other things, with the question of the influence of metabolic profiles on drug therapy safety in routine care. If the genome of a person is known, it is possible to deduce from their genetic predisposition how they are likely to react to a medicinal product. This makes it possible to predict whether certain side effects will occur or whether a therapeutic effect can be achieved at all. Such knowledge is of great advantage for the patients concerned, because it can help avoid unnecessary prescriptions and the occurrence of adverse drug reactions. On another level, it also saves the

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healthcare system costs, such as those incurred in treating side effects.

As a medical doctor who also studied computer science, Dr Steffens is perfectly suited to add his expertise in bioinformatics to the Pharmacogenomics Unit. "The real art is to find the best evaluation strategy and the most suitable algorithm for a particular medical problem or pharmacological issue, taking into account the available data and existing data structures," he says. Medical, statistical and IT expertise in AI methods are intertwined. "It is precisely this interface that makes our daily work so interesting. In my opinion, AI will not be able to replace physicians, but it will provide them with considerable support in diagnostics and therapy in the future. The evaluation of even more extensive and detailed data will make it possible to make even better prognostic and therapeutic decisions that are tailored to each individual patient."

The same applies to many areas of medicine. Pharmacogenomics is only one of these, but it is a very dynamic one. In recent years, the rapid progress in sequencing technology has made it possible to generate large amounts of pharmacogenetically and genomically relevant data.

The so-called EMPAR study is one example of how the BfArM is active in the field of pharmacogenomics. This study is concerned with the question of whether genetic differences have a recognisable influence on the claims made to the statutory health insurance services. As part of the study, the Research Division uses the AI computer to evaluate the medical data and metabolic profiles of more than 10,000 insured persons participating voluntarily in the study.

Another example of how the BfArM applies AI is the analysis of potential sources of failure in medical devices. Here, the occurrence of such so-called incident reports is analysed automatically. The developed programs and algorithms allow the conversion of risk-related information within free texts into structured data for examination.

Dr Steffens is convinced that AI applications will also increasingly find their place in regulatory work. For example, researchers are planning to develop a machine-learning model that will be able to assess reports on adverse drug reactions automatically and to recognise and classify the causal relationships between medication and adverse drug reaction. According to the scientist, "such a model might, for example, directly support regulatory assessment in pharmacovigilance".

The analysis and use of data with the help of AI methods is currently giving personalised medicine an enormous boost. The more and better data on the individual genetics of patients is available, the better the treatment can be adapted accordingly in the future. Thus, the risk-benefit assessments for

"Artificial Intelligence" and "Deep Learning"
Generally, the term "Artificial Intelligence" (AI) is often associated with intelligent speech assistants or image recognition programs. Usually, these are special machine learning processes based on artificial neural networks briefly summarised as "Deep Learning". A characteristic feature of this network architecture is that it consists of several hidden layers, which make it possible to extract properties from the data with increasing complexity. The AI computer at the BfArM is also suitable for such Deep Learning applications. Another major advantage of neural networks is that they are able to reuse knowledge once it has been learned, making future AI applications increasingly "intelligent".

therapeutic procedures are becoming increasingly individualised. "In the treatment of certain cancers, it is already common practice to determine selected genetic markers of patients in advance in order to align therapies and drug dosages accordingly," explains Dr Steffens. "Conversely, certain groups of substances, such as psychotropic drugs, are still mostly prescribed according to the trial-and-error principle." Valuable

time is often lost in this process; time that seriously ill patients do not have. "However, the trend is that in the not too distant future the entire genome of every patient will be known, which will yield the most important prognostic information for a wide range of medical questions."

Given that the human genome contains around 25,000 genes and consists of more than 3 billion base pairs, the importance of data analysis and the involvement of AI in this task is abundantly clear.

Michael Steffens, MD
University studies of Human Medicine and Computer Science. Employed at the Clinic for Diagnostic and Interventional Radiology of the University Hospital Bonn from 1999 to 2001 and from 2001 to 2011 at its Institute for Medical Biometry, Informatics and Epidemiology. 2010, research residence at the Wellcome Trust Centre for Human Genetics in Oxford. From 2011 to 2013, employed at the Institute for Medical Biostatistics, Epidemiology and Informatics at the University Hospital Mainz. Since 2013, at the BfArM's Division 5 "Research" in the Research Group Pharmacogenomics.

So we all know what we're talking about

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Digitalisation in the healthcare system would hardly be conceivable without semantics. On the basis of a uniform terminology, it is possible to process data automatically and even to search for specific patterns and information. The BfArM's experts in cooperation with the World Health Organization (WHO) are working on the development and worldwide advancement of corresponding systems.

For the layperson it is "chickenpox"; the physician's diagnosis is "varicella": for almost every disease and method of treatment there are different expressions that, although they have the same meaning, are not necessarily understood or interpreted in the same way by different people. Furthermore, such information including patient data can also take many different paths within the healthcare system. However, if an IT program only "knows" the medical term "varicella", it will not automatically be able to make the connection to "chickenpox".

In order for the right conclusions to be drawn from existing data, different systems must therefore be able to interpret the information in the same manner. This also applies to the research with such data with

the help of Artificial Intelligence. In order to search very large data sets for patterns related to a specific disease, the computers must also know alternative terms, e.g. for varicella.

The first step towards achieving this goal is the use of a uniform terminology, e.g. when diagnosing diseases. Dr Stefanie Weber, head of the executive department 'Classification Systems, Centre of Semantics' at the BfArM, has been working on the development and evolution of such systems for more than 15 years. "Our work is a necessary prerequisite for digitalisation and an efficiently controlled healthcare system," emphasises Dr Weber. The German Institute of Medical Documentation and Information (DIMDI) already had a special focus on this field of activity.

When the DIMDI was merged into the BfArM in May 2020, a declared goal was to advance this development further and in order to do so, the corresponding executive department was established. The aim was to make the best possible use of the synergistic effects in the areas of semantics and classification systems, thus strengthening both units. For instance, analytical processes and evaluation of healthcare data are ideally

"There is hardly any other country where the areas for applying the ICD-10 are as diverse as in Germany."

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combined through the expertise of data analysts. Our experts working in the newly established executive department are focused among others on the "International Statistical Classification of Diseases and Related Health Problems" (ICD). This system is used in Germany to encode diagnoses in outpatient and inpatient care. In addition to the translation and annual revision of this system, its further development and the search for new applications play an important role. The ICD is published by the WHO and is established in the healthcare system as an essential component for the documentation of diagnoses in billing, quality assurance and documentation systems. The German version of the ICD is abbreviated with the acronym ICD-10-GM ("German Modification"). It has been applied for about 20 years and is based closely on the WHO version in order to facilitate international comparisons and studies.

"In principle, our work can be compared to the creation of a dictionary," explains Dr Weber. "We collect and standardise several different terms for one disease. This allows a precise electronic exchange between all players." The keyword in this context is "semantic interoperability". Semantics defines terms, thus forming the basis for a corresponding terminology that defines diagnoses as specifically as possible and is equally comprehensible in all systems.

Such interoperability is becoming increasingly important for the healthcare system; without it, digital

health applications such as apps could not be used in an appropriate and efficient manner. In the future, such applications will communicate with each other and will also interact with other services and applications from our national eHealth infrastructure. Such a development will pose added value for future medical care.

Likewise, classifications are also important for statistical analyses. The cause-of-death statistics for Germany, for example, are based on the ICD. Scientific insight does not focus on one individual case but on the information that can be gained for a group of similar cases. In order to do so, individual cases have to be grouped together in groups or classes within the classification.

"There is hardly any other country where the areas for applying the ICD-10 are as diverse as in Germany," says Dr Stefanie Weber. The ICD-10-GM is not only relevant for statistics and billing purposes: Germany also uses this classification for sick leave slips, the prescription of remedies, aids and digital health applications, the quality assurance in hospitals and the reporting of infectious diseases, thus fulfilling a central key function.

Digitalisation does not stop at national borders. In order for patients in Germany to benefit from the potential of medical information, both from the European Union (EU) and from across the entire world, it will be essential to further develop classifi-

cation and semantics. Cross-border care and research on a European level require an ongoing exchange with our partners in Europe. Here, we are in close cooperation with international authorities like the European Medicines Agency and the WHO. "We are contributing our many years of expertise in all aspects of medical terminology here. We want to share our findings with the partner organisations in other EU countries in order to learn from each other and coordinate standardisation," says the medical expert.

BfArM experts, for instance, are involved in the development of the European Union's eHealth Digital Service Infrastructure. "This includes the creation of cross-national health services such as ePrescription or Electronic Health Records (EHR)," explains Dr Weber. For patients, this is supposed to ensure that their data can also be interpreted and understood accurately in the healthcare systems of other countries.

Furthermore, the BfArM is active in the so-called CoCoS (Corona Component Standards) Initiative, in which leading players in the healthcare system have joined forces. A wide variety of stakeholders, such as scientists and start-ups, are currently working on ways to research and handle Covid-19. It is the aim of the CoCoS Initiative to bring these projects together so that they can be made as effective as possible. This involves the establishment of uniform data formats and standards for interoperability for Covid-related data as well as the consolidation thereof.

The BfArM will continue to set strategic cornerstones in this field and will participate in the development and dissemination of classification systems and terminologies. Its long-standing commitment to international classification has also been recognised institutionally: the role as a collaborating centre for the WHO's system of international classifications assumed by the DIMDI in 2003 has now been confirmed for another four years. This expertise is now being further expanded under the umbrella of the BfArM as part of its digitalisation strategy.

Stefanie Weber, MD
MD certified in Medical Informatics. From 2002, scientific employee at the German Institute of Medical Documentation and Information (DIMDI) in the Classifications Department. From 2008, head of the "WHO Collaborating Centre for the Family of International Classifications". From 2010 to 2020, head of the Department "Medical Term Systems" in the DIMDI. From 2015 to 2018, chair of the WHO task force for the completion of the ICD-11. Since 2020, head of the executive department "Classification Systems, Centre of Semantics" at the BfArM.

Opportunity for pharma-ceutical regulators

Healthcare data is naturally not only generated in Germany, but on a global level as well. For the European medicines regulatory network, this poses enormous potential, for example, to support regula-tory decisions with evidence from medical practice. The BfArM is part of this network and is involved in the development of appropriate concepts to allow for the efficient use of such data.

In the future, the use of healthcare data will have a major impact on the work of drug regulatory author-ities, both on national and European levels. Such data from the "real world" (hence, "Real World Data" or RWD for short) is generated every day in all countries of the European Union (EU), e.g. in terms of health insurance data, based on reports of adverse drug reac-tions or through the use of "medical apps". "Big Data" is the name given to this huge amount of data that basically has the potential to provide targeted support for the assessment of efficacy and risks. In its raw state, this data is complex, unstructured and heteroge-neous and must therefore be processed using specific methods before it can yield reliable analytical results; only then can we detect patterns or correlations.

"We must not let this potential go unused; instead we must work together to achieve the best possible benefit from Real World Data for drug regulation," says Dr Martina Weise, Head of Licensing Division 2 at the BfArM. For more than ten years, the physician has been active in the Committee for Medicinal Products for Human Use (CHMP), which is one of the most important scientific committees of the European Medicines Agency (EMA). Supported by experts from national authorities, the CHMP members deliberate on the benefits and risks of medicinal products in the EU. For Dr Weise, it is a logical consequence that the use of technological innovations will suitably support the future scientific work of these committees, e.g. the benefit-risk assessment of medicinal products.

Both the evaluation of risk-benefit ratios and the preparation of corresponding scientific assessment re-ports on medicinal products are among the core tasks of the CHMP – not only during the marketing author-isation procedure but also continuously throughout the entire life cycle of a medicinal product. In this, the CHMP cooperates with another of the EMA's committees, the Pharmacovigilance Risk Assessment Committee (PRAC). Among other things, the PRAC

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performs regular analyses and evaluations of adverse drug reactions. In doing so, it draws on a European database in which all reports of such adverse drug reactions are collected. These reports are submitted, for example, by physicians, pharmaceutical companies or the patients themselves. The PRAC also evaluates post-marketing surveillance or observational studies, which can provide a wide range of information about pharmaceuticals in the real world.

"Basically, we are already using data from the real world, in particular to track the safety of medicinal products after approval," explains Dr Weise. According to the physician, randomised controlled trials are still the gold standard for the evaluation of efficacy. "In order to make Real World Data more usable for our purposes, standards must be established for, among other things, identifiability, quality, interoperability and verifiability of the data, as well as for analytical methods." The significance of Real World Data could be further increased if we were able to use sources from different EU countries. "The more data on a medicinal product we can analyse specifically, the more solid is the foundation upon which we base our decisions."

The idea of what licensing and monitoring of medicinal products may look like in the future is thus already very specific. In order to benefit from all this data and to use it prudently, regulators obviously need the appropriate analytical methods and technical expertise.

The "Task Force on Big Data" works at shaping this development on a European level. It was introduced in 2017 by a consortium of the national regulatory authorities "Heads of Medicines Agencies" (HMA) and the EMA in order to identify the challenges and the potential that large amounts of data pose for drug regulation. The task force is composed of experienced drug regulators and data experts appointed by the national competent authorities, the EMA and the European Commission. Furthermore, the CHMP has established a "Digital Therapeutics Group", of which Dr Martina Weise is a member. This group deals with the increasing number of applications for combinations of medicinal products and digital medical devices (mainly medical apps) and establishes criteria for their evaluation.

Among other things, the members will focus on the issue of how best to use the large amounts of data to support innovation and public health in the EU. One important element in this connection is to standardise content and achieve interoperability. To this end, the establishment of a common EU platform to provide access to health data from across the EU is being discussed. The project called "DARWIN" ("Data Analysis and Real World Interrogation Network") aims to create a European network of databases. The content of these databases must ensure the highest

level of quality and data security. This way, regulatory decisions could be confirmed by robust evidence from medical practice.

One thing is certain: the technological developments in the healthcare sector will definitely have an impact on the work of regulatory authorities. However, Dr Martina Weise does not believe that the scientific work of the EMA committees will eventually become superfluous due to the new technologies. On the contrary: "Its tasks will become more complex and additional expertise will be required, especially in the field of advanced statistical methods," says the physician. "Once we have the right requirements to be met by the data, the next step is to draw the right conclusions from them."

Since patients are not randomly assigned to treatment groups as would be the case in randomised trials, all types of bias can occur, which must be identified and minimised. Otherwise, there is the danger that efficacy is wrongly attributed to the medicinal product under investigation or that an actual effect is not recognised, according to Dr Weise. "Further development of the expertise in analysis and interpretation of Big Data will ensure that the EU network can make the best possible use of this information."

Currently, the physician does not see Real World Data rendering randomised, double-blind, controlled clinical trials redundant. "At the moment, the aim is to use this data to generate additional evidence that can further improve our decisions for the benefit of the patient." According to her, single-arm studies and a comparison with Real World Data, such as "natural history data", are already accepted in cases where it is difficult or impossible to conduct randomised controlled trials, e.g. in very rare diseases.

The BfArM will continue to contribute its expertise in this field in order to advance new therapeutic options and to make the benefits of digitalisation available for the care of all patients.

Martina Weise, MD
MD specialised in Paediatrics. From 1996 to 2001 Fellowship in paediatric Endocrinology at National Institutes of Health, USA. Joined the BfArM in 2001, first as head of the "Endocrinology/Gynaecology" Unit, later of the "Diabetes/Cardiovascular System" Unit. Since 2016, head of the Division "Licensing 2". Since 2009, alternate member, and since 2018, German full member of the Committee for Medicinal Products for Human Use of the European Medicines Agency (CHMP).

Combining traditional tasks with new topics

The work of the BfArM is intermeshed to a large extent with scientific and technical innovation: medical progress is taking place in ever shorter intervals and digitalisation is creating new impulses in almost all fields of activity. What's more, patients have the legitimate expectation that they will be benefiting from innovations in the healthcare sector without unnecessary delays.

In the licensing of medicinal products, the BfArM is in high demand with potential applicants seeking scientific and procedural advice. Nationally, **+343 applications** for advice were processed in 2019, while by October 2020 there were **+273**. At the level of the European Union (EU), BfArM experts participate in advisory procedures in the Scientific Advice Working Party (SAWP) of the European Medicines Agency (EMA): in the year 2019 they were active in **+117** of a total of **+608 advisory procedures**, and in 2020 (as of October) in **+90 such procedures**.

Exponentially increasing data volumes ("Big Data", "Real World Data") and the use of Artificial Intelligence (AI) in the healthcare system are also influencing aspects of the regulatory and scientific tasks of the

Federal Institute. For example, the BfArM already uses AI computers to search large data sets for patterns that can provide valuable findings with regard to e.g. pharmacotherapeutic safety. Such "Big Data" also plays a significant role in the field of medical devices: approaches to data-supported risk signal detection are being developed which can be incorporated directly into a risk assessment for the safety of medical devices.

In 2019, the BfArM received **+17,905 such risk reports**, both from Germany and from other countries. On the basis of these reports, recommendations can be made to eliminate, reduce or prevent the recurrence of the risks observed.

"We are focusing in-depth on these new opportunities," says the BfArM President. "In doing so, we are automatically keeping an eye on the development of concepts for the entire EU. The aim is to pave the way for joint use of health data, such as the information generated in everyday care." Interoperability and the standardisation of scientific information are important building blocks in this context. In order to create synergistic effects on this level, the BfArM and essential functional units of the German Institute

of Medical Documentation and Information (DIMDI) were merged into one authority under the umbrella of the BfArM in May 2020. The advantages of joining forces with such a highly specialised provider of scientific services will directly benefit patients.

With regard to patient safety, the reporting of so-called "adverse drug reactions" (side effects) continues to play a major role. Both the BfArM and the Paul-Ehrlich-Institut (PEI) are dependent on reliable data from medical practice in order to identify possible risk signals, for example regarding previously unknown side effects of a medicinal product. The two authorities provide a modern and barrier-free reporting portal for this purpose at www.nebenwirkungen.bund.de. Suspected cases are entered into the "European Database of Suspected Adverse Drug Reaction Reports" where they can be accessed quickly, directly and reliably by the pharmacovigilance experts. In 2019, this database recorded a total of **+1,227,930 cases of adverse drug reactions** (ADR for short), **+128,933** of which were reported from Germany. **+83,054** of these were spontaneous ADR reports, meaning that they occurred outside of studies, in the routine handling of medicinal products; of these, **+23,289** were classified as serious.

The BfArM itself has for many years recorded a sustained trend of significantly increasing numbers of direct reports. The number of such direct reports by health professionals rose from **+6,906 reports** in 2012 to **+11,010 reports** in 2019, an increase of **+37.3 percent**. The number of direct reports from patients, their relatives and legal representatives even grew by more than **+1,500 percent** in the same period (number of reports in 2012: **+310**; number of reports in 2019: **+4,832**). The European medicines authorities support this reporting behaviour and encourage the consolidated reporting of suspected ADRs in an annually launched social media campaign. **+57 medicines authorities** worldwide already participated in the fourth such campaign in 2019.

As a further approach to increase the safety of medicinal products and medical devices and thus patient safety, the BfArM is a partner in the innovation project "Giga for Health" to develop an app for reporting risks related to medical devices. The aim is to be in a better position to evaluate risks on the basis of these reports and to initiate effective safety measures even faster in cooperation with manufacturers and the German "Land" authorities.

Additionally, the BfArM's role with regard to shortages in the supply of medicinal products has also been consistently reinforced and enshrined in legislation. In July 2020, the "Jour Fixe on Delivery and Supply Shortages" was institutionalised in a statutory advisory board meeting in accordance with Section 52b sub-section 3b of the German Medicinal Products Act. It is the task of this committee to continuously monitor and evaluate the supply situation of medicinal products intended for human use. The BfArM itself now has the power to order quotas and stockholding measures in case of an imminent supply shortage. The German Federal Government has made the issue of the production of medicinal products within the EU a major focus of its EU Council Presidency.

The BfArM supports this initiative to strengthen the production of supply-relevant medicine within the EU, in order to counteract an increasing monopolisation and to lessen dependencies on individual economic areas.

The Federal Institute is also setting new standards with regard to the Cannabis Agency, which made it possible to implement the cultivation of pharmaceutical grade cannabis in Germany under adherence to the legislation on narcotic drugs and medicinal products. The procedure for granting cultivation permits was successfully completed in 2019. The BfArM will purchase the medical cannabis cultivated in Germany, take legal possession of it and resell it to manufacturers of medicinal cannabis products, wholesalers or pharmacies. In this way, the BfArM will make an important contribution towards improving the supply situation in Germany.

Furthermore, importing medical cannabis into Germany will continue to be both possible and necessary. The Federal Opium Agency at the BfArM issues the necessary licenses and authorisations for such imports, but does not have a central control function with regard to the imported quantities. The cultivation of cannabis for medical purposes, on the other hand, is controlled by the Cannabis Agency and is monitored (among others) by the Federal Opium Agency.

+6,744 kilograms of cannabis flowers were imported to Germany in 2019, compared to **+4,126 kilograms**

in the first two quarters of 2020. The Federal Opium Agency also ensures that patients are safely supplied with medically necessary narcotics. In 2019, approximately **+15 million** prescription forms for narcotic drugs were sent to physicians – an increase of around **+1 million** compared to the previous year. "The Federal Opium Agency deals specifically with the needs and issues of the healthcare system," says Professor Broich. "Our aim is to develop pragmatic solutions together." For example, the BfArM was also commissioned by the Act on the Amendment of the Narcotic Drugs Act and other Provisions ("Gesetz zur Änderung betäubungsmittelrechtlicher und anderer Vorschriften"), which came into force in 2017, to conduct a non-interventional concomitant survey on the use of medical cannabis products. This survey will be conducted until 31 March 2022; the initial results have already been published.

In the European network of drug regulatory authorities, the BfArM has further expanded its position as one of the leading partners. In particular, after the withdrawal of the British regulatory authority from the European licensing scene, the Federal Institute took on numerous additional centralised authorisation procedures and due to its expertise has been increasingly sought out by the pharmaceutical industry as a Reference Member State in decentralised procedures; by 2019, it had evaluated **+225** (**+22 percent)** of these procedures in the EU. Now, as of October 2020, the number of DCPs (decentralised procedures) stands at **+160** (**+24 percent)**.

ed measures and objectives in order to react promptly and efficiently to innovations and challenges as well as to current health threats. Since _33_ 1994, the BfArM has b

The BfArM also contributes its expertise to centralised authorisation procedures through which innovative drugs are approved in all Member States of the European Economic Area. In 2019, +178 of these so-called rapporteurships were assigned, +18 of which were allotted to Germany, and of these, +10 went to the BfArM. As of September 2020, Germany has assumed +13 of +122 rapporteurships for innovative medicines, +9 of which were submitted to the BfArM. In both years, the Federal Institute thus occupied top positions among the European licensing authorities.

Among other things, the BfArM was also the rapporteur in the EMA's approval procedure for Remdesivir. This medicinal product was approved in Europe in July 2020 under specific conditions as the first therapeutic drug for the treatment of Covid-19. With a view to possible therapeutic options in connection with the coronavirus, the Federal Institute is also monitoring a number of clinical trials, providing information on off-label use and compassionate use. Clinical trials are an essential prerequisite for the development of new medicines. In 2004 it became mandatory for such studies to be approved by the authorities in Europe. Since then, the BfArM has issued more than +13,000 such authorisations. In 2019, the BfArM received +649 applications for authorisation of a clinical trial; as of September 2020, +428 applications have been submitted.

Hardly any other topic in the coming years will have as much of an impact impact on the work of the BfArM as digitalisation. It holds enormous opportunities for the development of new therapies and efficient healthcare. The Federal Institute has clearly positioned itself in this field from the outset and acts as a reliable partner in the digitalisation strategy of the Federal Ministry of Health. When the Digital Healthcare Act came into force in December of 2019, the "app on prescription" for patients was introduced into the healthcare system. This means that around +73 million people insured under the statutory health insurance scheme are entitled to digital health applications (DiGA), which can be prescribed by physicians and psychotherapists and reimbursed by the health insurance. Within a very short period of time, the BfArM set up a corresponding test procedure for this purpose and created the list of reimbursable DiGA. "We are focusing strongly on the potential that digitalisation offers," says Professor Karl Broich. "The BfArM acts as an impulse generator, helps shape processes and occupies a leading position in this domain."

Against this background, the BfArM's Innovation Office, which was already established in 2017, has proven its worth as an orientational information and consulting service. It has become an uncomplicated first point of contact for those who need assistance with regard to the formal requirements of the healthcare market. In addition to a large number of daily telephone calls, the Innovation Office has received about +900 written enquiries since the end of January 2017 and approximately +220 applications for kick-off meetings. +57 such meetings were held in 2019 and +84 in the year 2020 (as of October of that year).

"The DiGA directory particularly benefits from these advice procedures," according to the BfArM President. "We are fulfilling our role as facilitator and are setting

the pace to support manufacturers, start-ups and developers on their way towards becoming suppliers."

The use of technical and linguistic standards is a crucial factor for ensuring that digitalisation in the healthcare sector can unfold its potential. The BfArM contributes to the establishment of interoperability in this area, e.g. by providing the German edition of the medical terminology SNOMED CT and by publishing the German disease classification systems.

In all these respects, the Federal Institute is a strong and reliable partner in the European network for the licensing of medicinal products. "The corona pandemic has once again made it clear how important it is for us in Europe to act together," emphasises the BfArM President. Of course, the authorisation of medicines and the improvement of their safety, the risk assessment and evaluation of medical devices as well as the monitoring of the legal traffic in narcotic drugs and precursors will continue to be an important part of the Federal Institute's core activity. "For us, these new topics represent new opportunities not only to assist us in these tasks, but also to drive them significantly forward. The primary goal of all the measures we take is and remains to increase the safety of medicine and thus also that of the patients."

Further figures and statistics can be found at:
www.bfarm.de/statistiken