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Building a DiGA – an IT and Medical
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Digital Health Applications (Digitale Gesundheitsanwendungen—DiGAs): Digital Drugs on the Horizon

Building a DiGA—an IT and Medical Multidisciplinary Venture

As part of our second article on “Digital Health Applications” we illustrate the multidisciplinary venture of building a Digital Health Application (DiGA). Assessing a health related outcome does not transform a mobile application or a software into a DiGA. Hence, elevating an app to DiGA level means state-of-the-art-upgrade of the two major pillars—the IT platform and the content—of a health application. Several legal requirements and regulatory expectations are to be met by both these components (separately and in conjunction) before the app will be authorised as a DiGA. In contrast to a simple health related app, where the IT platform and the content can be freely developed, in case of a DiGA this is much more complicated, requiring careful planning and execution of all necessary steps. It’s an endeavour which introduces the app development company into the interesting world of the medical, pharmaceutical and clinical research, while forces the health and pharmaceutical companies to dive into the technical environment of the IT sector. Despite, both these industries require innovation and high-level training in their particular field, when it comes to development of a DiGA, intersection of the personnel of two giants is needed, which might be sometimes challenging. These challenges can be overcome only by putting together a multidisciplinary team, comprising the best specialist from both parties.

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Background

As mentioned in our last article “Digital Health and Digital Treatments: The New Reality” (PM QM 2020, 22/3:134–139) [1] a DiGA is considered as a very special software, while others would consider it a special medical device or a treatment, comparable to drugs. Actually, a DiGA is a combination of all these: it is a software by its nature,

it’s a medical device by its function and can be a treatment by its effect [2][3][4]. Therefore, it is often challenging for an applicant to decide by itself whether the digital technology developed falls under the definition of a DiGA and by this under European Medicines Agency’s (EMA’s) remit [3][5]. A precise definition would be of help in such cases, but this is not provided by the regulatory authorities. Ultimately, this is

an understandable approach, as both EMA and U.S. Food and Drug Administration (FDA) would like to avoid the exclusion of innovative approaches that might arise in time [5][6]. In the absence of a clear and precise definition, the manufacturer and developer of a future DiGA needs to go step by step through a decision chain about the Medical Device Classification of the developed digital technology, characteristics of the IT platform used, core of the app, compliance with the General Data Protection Regulation (GDPR), and characteristics of the content of the app [2].

Classification of the digital technology

Smart devices and smart applications make the life of patients and healthcare providers easier. Digitisation of the healthcare is not a luxury anymore, but an urgent demand coming from all stakeholders. Accordingly, software development companies are attracted, invited or sometimes forced to take part in this digital revolution [7]. The increasing number of players



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results in a healthy competition, which ultimately widens the area of interest of these software developers. It is unavoidable for a software development company creating digital technology for drug development or for medical devices used exclusively by physicians, to come to a point where they would want to address directly to the patient. At this point such a company will decide on developing a DiGA. But planning and building a software capable to improve the health of a human being is only the first step. Once the development plan or the software is ready, the developer needs to classify it according to the European Medical Device Regulation (EU MDR) Classification Rules [3][8]. This, however, can become a challenging task, especially that new EU MDR changes are expected during 2021. It is to be noted, that the entry into force of the EU MDR has been postponed from 26 May 2020 to 26 May 2021, due to the COVID-19 pandemic. The EU MDR will contain 22 rules for classification—four more than the previous European Medical Device Directive (EU MDD) [5]. All of the rules are based on the potential risks associated with the device, its technical design, and how the device is manufactured. Under the new regulation, it is important to understand the EU MDR classification rules and the rules surrounding the classifications [3][4][5][8][9].

So, how to answer easily what EU MDR class the intended DiGA is? A simple decision pathway is provided within Figure 1.

It should be noted that currently only software that belongs to the lower risk I or IIa medical device classes can be considered a DiGA. This is due to the novelty of digital health applications on the European health market, yet imposing a need to minimise the risk to patients as much as possible [2]. As presented within Figure 1, clear rules are used to classify a software in this regard. One of the most important to be considered is the EU MDR [3].

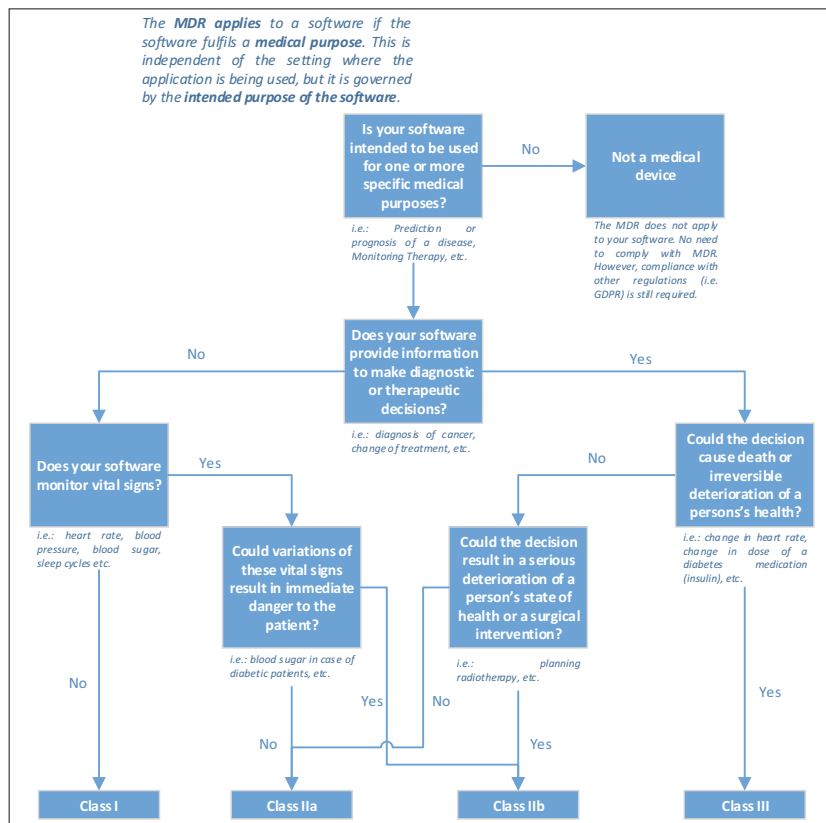


Figure 1: EU MDR Decision Pathway—“what MDR class is the intended DiGA”

Paragraph 3.3 of the EU MDR states that software, which controls a product or influences its use, is assigned to the same class as the product. In addition, if a software is independent of other products, it is classified on its own. A software is considered a DiGA when uses external devices as an interface but produces effects independently from the interface (same effect will be produced on different interfaces). Accordingly, the benefit of the software is paramount, and therefore the second part of implementation rule 3.3 must be applied to it. The software is thus classified on its own [3][5].

Even if currently a DiGA can be of only Class I or IIa, it is still challenging to decide which group the DiGA will fit in, as this decision needs to consider not just the software itself, but also the device the software is used on.

For example, rule 11 of the EU MDR guideline states: “Software intended to provide information used to make decisions for diagnostic or therapeutic purposes is classified within Class IIa unless those

decisions have consequences that may cause: death or irreversible deterioration of a person's health, in which case it is to be classified in accordance with Class III, or serious deterioration of a person's health or surgical intervention, in which case it is in Class IIb” [3].

In addition, rule 9 of the aforementioned EU MDR regulates any software that controls a product or influences its use. It states that all active devices which are intended to control, regulate or directly influence the performance of active therapeutic devices of Class IIb or for the emission of ionizing radiation must overall be assigned to Class IIb. Accordingly, no software running on a Class IIb medical device or on devices emitting ionizing radiation can be considered a DiGA [3].

Considering these rules in conjunction with the German Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte —BfArM) requirements for a DiGA (“the DiGA supports the detection, monitoring, treatment or allevia-

tion of diseases or the detection, treatment, alleviation or compensation of injuries or disabilities”) it very quickly becomes clear that DiGA can only be assigned to Class I in a few cases, while most of DiGAs will pursue a diagnostic or therapeutic purpose in order to be listed as such by the BfArM [2].

The two pillars of a DiGA

Building up a DiGA is not a simple task, and as was mentioned in the introduction of this article, quite often a multidisciplinary team is needed to support its development. The magnitude of this challenge can be understood when looking to the structure or the frame a DiGA is built on. Basically there are two major pillars: an IT platform and the content of the software. None of these two could be accepted alone as a DiGA. The IT platform without a proper medical content it’s just a simple software, while the medical content without an IT platform is only an information which cannot reach or help a patient. Therefore, these two need to merge in a harmony, and need to meet all regulatory criteria both individually and combined, to finally be accepted as a DiGA [10][11][12].

Characteristics of the IT platform of a DiGA

In EU countries, the most important prerequisite for approval of a software as a medical device is the CE certification. The BfArM, however, places more high technical demands when a software is to be approved as DiGA. In addition to the efficacy and safety-related endpoints (similar to the EU MDR requirement), these include all the usability (user experience) endpoints of the respective product. For example, the application must ensure sufficient backup options to prevent data loss. Transmission errors and faults must also be taken into account so that a loss of internet connection or power supply can be bridged and no data loss or data corruption occurs. Technically, this

must be mapped by an extensive infrastructure and by corresponding code adaptations. In addition, these need to be tested extensively and continuously. The manufacturer is expected to conduct an intensive analysis, since each software must meet different technical requirements and the measures have to be therefore individualised. Such measures can be the possibility of resetting the app by the user, or plausibility checks preventing incorrect entries and thus increasing usability [1][2][13].

Another important criterion the IT platform of a DiGA needs to address is user awareness. Users should be informed at all times about the functionalities of the software and if necessary, be able to consult with a support person (i.e. technical support, health related or medical support, social support, etc.). To this end, external devices such as smartphone cameras or wearables must be integrated into the application [2][14][15].

These and other measures are designed to detect and prevent risks, ultimately ensuring the increased safety of patients, which always comes first.

In addition to the already ruling EU MDR and BfArM DiGA regulations, another, yet drafted BfArM law primarily envisage the electronic patient record (ePa) and the telematics infrastructure. DiGAs are therefore expected to be interoperable, so that interfaces between the various systems can be ensured in order to communicate with each other. The BfArM is taking an important step here, elevating interoperability to an essential quality feature. Accordingly, all applications must be able to communicate with each other to ensure that data can be presented in human-readable and printable form in the future, and used by physicians as well as patients. One example is the online platform “Vesta”, which provides predefined values in form of guidelines regarding exchanged data. The given example is not randomly chosen, as it is regarded as a central and independent direc-

tory for IT standards in the German healthcare system. [2][7][16]

In addition, other medical devices or sensors (wearables) should be able to interact with the applications via interfaces. However, the most important factor for interoperability is the connection to ePa, as this will be the central interface of medical documents in the future.

Success story—Interview

One of the ten companies (as of 10 January 2020) that has already mastered all challenges and is now sustainably listed in the DiGA directory of the BfArM is mementor GmbH with its product somnio [16][17].

A five question interview was conducted with Mr Noah Lorenz, founder and CEO, mementor GmbH, to evaluate some of the major challenges in the endeavor of research, development and approval of their DiGA:

For which patients is your digital health app somnio suitable and what is it based on?

Noah Lorenz: Somnio is a digital sleep training for patients that are suffering from insomnia. It is based on cognitive behavioral therapy, an evidence-based therapy that is recommended by international guidelines as the first line treatment for insomnia disorder.

What has been the biggest challenge for you within the process of certification to be listed as a DiGA?

Noah Lorenz: As we were one of the first companies to undergo the fast-track procedure of the BfArM, the biggest challenge was to independently build up know-how and expertise on the requirements and to take these requirements into account technically in our product and beyond.

How did you do the analysis to anticipate potential misuse of the patients and improve the user experience?

Noah Lorenz: Since we were already able to gather market expe-

rience in advance, e.g. through user and usability tests, we were quite well prepared. In addition, we were able to gain some experience with patients in advance through a Randomized Controlled Trial (RCT) study conducted at the University of Zurich [17].

How have the recent changes regarding the US Privacy Shield affected you ?

Noah Lorenz: The biggest change was that from one day to the next no personal data could no longer be stored on servers of companies that are subsidiaries of a US holding company. Even if these companies are located in the EU and the servers in Germany. For some DiGA manufacturers this was a major problem, some had to change their hosting provider. Fortunately, this affected us less because of our non-US hosting provider.

GDPR compliance

The aforementioned technical expectations must be completed by specific data protection capabilities when applying software for being recognised as a DiGA. These capabilities need to follow the legal requirements of the GDPR and the Federal Data Protection Act (Bundesdatenschutzgesetz—BDSG). By using the checklist of Appendix I of BfArMs’ DiGA guidelines, compliance with data protection is assured by 40 statements relating to both the technical implementation of the DiGA and the organisational aspects [2].

Two overarching aspects are to be noted here:

- the permissible purposes of data processing and
- the non-permissibility of processing abroad.

These first essentially state that all protective measures must be observed and that careful handling of individuals’ data must always be ensured. In addition, the processing of personal data requires the explicit consent of the person.

The non-permissibility of processing abroad (based on article 46 GDPR) generated several legal discussions and contradictions within the last months [18]. For example, the law “Privacy Shield Agreement”, relevant for DiGA [19], was declared invalid by the European Court of Justice (ECJ) agreement on 16 July 2020, as the provisions of the guide are contradicting this law. As per the ECJ, processing of personal data outside the EU is not permitted under the DiGA Fast Track Guide, since the US law cannot adequately ensure protection of EU personal data. This means that even clouds of large US technology companies such as Microsoft, Google, and Amazon cannot store personal data coming from DiGA. The implications are immense as many interfaces work with cloud services such as Amazon Web Services (AWS), Google Cloud or Microsoft Azure [19].

DiGA manufacturers will have to rely on EU located IT systems to host their personal data. This can become a pitfall, as such systems are not easy or cheap to be built up and to sustain. There are a series of requirements such an IT infrastructure needs to comply with:

- Premium level secure data storage and access
- Safe and constant backup of data
- Zero or no downtime

There are companies however, which already have such an IT infrastructure in place, prepared for hosting databases used in clinical research, drug development and implicitly by DiGAs. For example, CCR GmbH has built an infrastructure that is fully and cost-effectively maintained within the European region in fully owned servers for maximum data security, along with a redundant architecture to

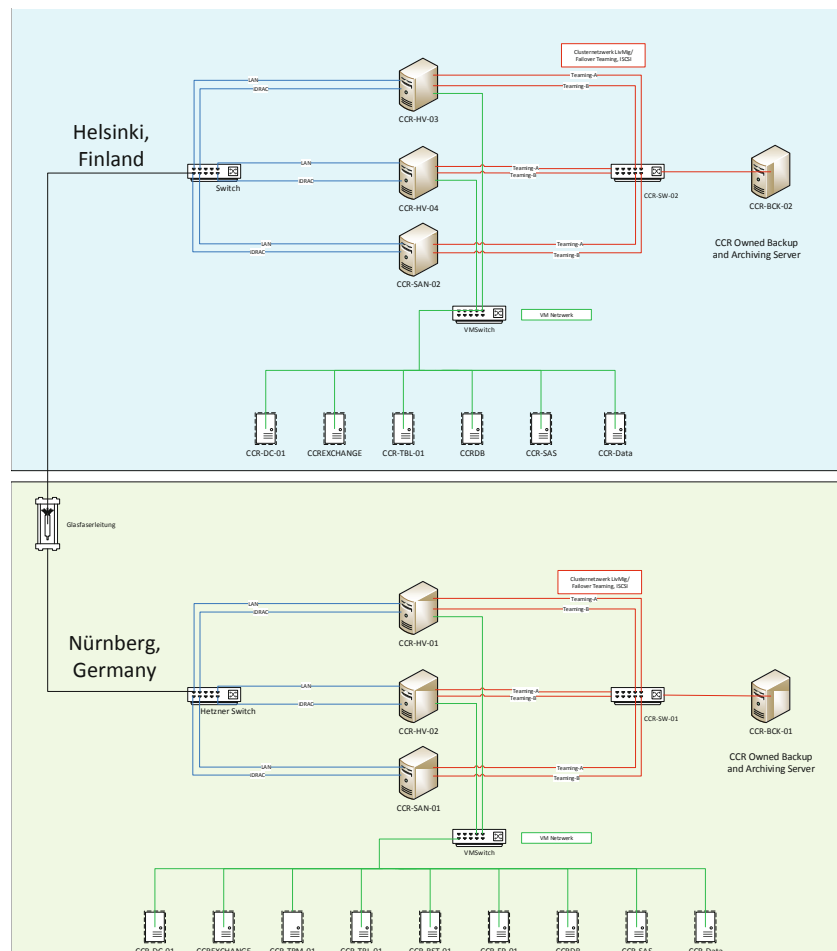


Figure 2: CCR EU IT Infrastructure

avoid any data loss or downtime. Figure 2 presents this as an example.

Characteristics of the content of a DiGA

The second pillar of a DiGA is given by the health-related content, which fills the IT platform and uses it to gather data about the patient. Besides gathering structured health-related data, content of the DiGA can be set up in an interactive way, so that it ultimately provides also a feedback to the patient, and actively supports patient’s health. At the end, there are myriad of possibilities on how the content of a DiGA could be set up. Nevertheless, there are some characteristics, which need to be met in order to achieve regulatory approval and reimbursement [2][20].

Patient centricity is the core requirement of a DiGA’s content. As defined by its name, in a patient centred care the patient’s needs, desires and feedback are behind all health decisions. Accordingly, a DiGA needs to primarily focus on the patient. Therefore, when setting up the content for a DiGA it is utmost important to consider that digitization and patient centred care resulted in a new type of healthcare user: the e-patient. “An e-patient is a health consumer who participates fully in his/her medical care, primarily by gathering infor-

mation about medical conditions that impact them and their families, using the Internet and other digital tools.” The “e” can stand for “electronic” but lately was used also as “equipped”, “enabled”, “empowered” and “expert” [14][20][21].

According to the Picker Institute [20] there are eight principles or eight expectations a patient would like to be fulfilled when it comes to Person Centred Care:

- Fast access to reliable health care advice
- Effective treatment delivered by trusted professionals
- Continuity of care and smooth transitions
- Involvement of, and support for, family and carers
- Clear information, communication, and support for self-care
- Involvement in decisions and respect for patient’s preferences
- Emotional support, empathy and respect
- Attention to physical and environmental needs

Based on the above it can be easily understood, that the content of the DiGA has to focus on data gathered primarily from the patient. In addition it is highly advisable to involve other parties like family members or healthcare providers, and by this widen and improve patient’s health related experience.

Beside patient centricity, a DiGA needs to be efficient and need to meet certain safety criteria.

Efficiency of a DiGA is translated by the health benefit provided. In general there are three types of health benefits which could elevate an app into a DiGA.

- The positive impact of a device on the health of an individual, expressed in the terms of a meaningful, measurable, patient-relevant clinical outcome(s), including outcome(s) related to diagnosis
- The positive impact of a device related to its function, such as that of screening, monitoring, diagnosis or aid to diagnosis of patients
- The positive impact on patient management or public health.

So, what kind of outcomes should a DiGA provide? To achieve the level of a DiGA, the central parameters of a software should focus on numerous aspects as shown in Table 1.

In addition to patient centricity and efficient health benefit, the third characteristic which transforms a simple software to a DiGA is the app’s safety. Some might ask, how the safety of a software can be tested. There are three types of safety outcomes which can be and need to be tested in case of a DiGA: safe use of the app, safety profile of the outcome and overall safety of the patient. Of course not all three are always applicable to all DiGAs. It might happen that one or another of these safety endpoints are

Patients’ physical status (i.e. disease progression, efficacy of treatment, etc.)	Patients’ mental status	Quality of Life (QoL)	Healthcare cost reduction
<ul style="list-style-type: none"> • Disease progression • Efficacy of treatment/ medication • Compliance • Laboratory values • Clinical parameters (blood pressure, heart rate, etc.) • Physical activity • Demography data (weight, BMI, nutrition, etc.) • Smoking status, alcohol consumption, drugs, etc. 	<ul style="list-style-type: none"> • Mental hygiene • Montreal Cognitive Assessment (MOCA) • Mini-Mental State Examination • Depression • Others 	<ul style="list-style-type: none"> • Quality of Life Scale (QoLS) • EQ-5D (Euro QoL) • Short Form Health 36 (SF-36) • Other standardised questionnaires 	<ul style="list-style-type: none"> • Hospital admissions • General practitioner (GP) visits • Patient flow • Patient „journey“ • Scheduling & staffing • Etc.

Table 1: Examples of central domains and parameters of a DiGA

tested. Anyway, the safety of each DiGA has to be proven following the BfArM guideline [2].

What exactly each of these safety profiles mean? Safe use of the DiGA refers to possible effects of the DiGA usage on the safety of the patient. For example, in case a DiGA provides a feedback related to weight of a patient, the user might get happy or pleased and also sad or depressed by the outcome the DiGA provides. The experienced depression would be considered a DiGA related safety event. On the other hand, in case the DiGA intends monitors or follows a connected device or procedure, the safety profile of this device or procedure can be established. This will represent the safety profile of the outcome. For example, if the DiGA helps a diabetic pa-

tient with insulin pump to create and report his blood sugar profile, than the safety profile of the insulin pump can be recorded using the DiGA. Finally, the overall safety of a patient would be represented by all the adverse events experienced during use of a DiGA, with no regard to causality and severity.

Obviously, during the research and development as well as within the post-authorisation use of a DiGA the main safety related focus will be on the first type of safety events, namely the “safe use of the app”. In addition to possible adverse events caused by the content of the DiGA, there are a series of software related events which might be considered as safety issues [3][13]:

- **Incident**—any malfunction or deterioration in the character-

istics and/or performance of a device, as well as any inadequacy in the labelling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a patient, or user, or of other persons, or to a serious deterioration in their state of health.

- **Malfunction**—the failure of a device to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labelling for the device. The intended performance of a device refers to the intended use for which the device is labelled or marketed.
- **Use Error**—user interaction or lack of user interaction while using the device that results in a device response that is different

Name of DiGA	Indication	Type of authorisation	Manufacturer
elevida	Multiple sclerosis	Permanent	GAIA AG, Germany
Invirto	Agoraphobia: Without mentioning a panic disorder Agoraphobia: With panic disorder Social phobias Panic disorder [episodic paroxysmal anxiety]	Temporary	Sympatient GmbH, Germany
Kalmeda	Tinnitus aurium	Temporary	mynoise GmbH, Germany
M-sense Migraines	Migraine	Temporary	Newsenselab GmbH, Germany
Rehappy	Transient cerebral ischemia and related syndromes Subarachnoid hemorrhage Intracerebral hemorrhage	Temporary	Rehappy GmbH, Germany
Selfapy's online course for depression	Slight depressive episode Moderate depressive episode Other depressive episodes	Temporary	Selfapy GmbH, Germany
somnio	Inorganic insomnia	Permanent	mementor DE GmbH, Germany
velibra	Agoraphobia: With panic disorder Social phobias Panic disorder [episodic paroxysmal anxiety] Generalised anxiety disorder	Permanent	GAIA AG, Germany
Vivira	Primary coxarthrosis, bilateral Other primary coxarthrosis Coxarthrosis as a result of dysplasia, bilateral	Temporary	Vivira Health Lab GmbH, Germany
zanadio	Obesity	Temporary	aidhere GmbH, Germany

Table 2: DiGA Success Stories—10 January 2021

from the response intended by the manufacturer or expected by the user.

- **Usability Issue**—any report received from a third party (written, electronic, verbal communication) about a use error or customer satisfaction issue by the user of a medical device or a combination product.
- **Product Technical Complaint (PTC) [22]**—any report received (written, electronic or verbal communication) about a potential or alleged failure of a product in its quality (including the identity, durability, reliability, safety, efficacy or performance) or a suspected counterfeit. The complaint may or may not represent a potential risk to the patient/customer/user/environment.

All these events can appear unanticipated or anticipated. A deterioration in state of health is considered unanticipated if the condition leading to the event was not considered in a risk analysis.

Similarly, they can be considered non-serious or serious. In the context of a DiGA, serious adverse event/incident/injury means any event/incident/injury that led to a death, injury or permanent impairment to a body structure or a body function or led to a serious deterioration in health of the subject, that either resulted in a life-threatening illness or injury, or a permanent impairment of a body structure or a body function, or in-patient hospitalisation or prolongation of existing hospitalisation, or in medical or surgical intervention to prevent life threatening illness [3][4][5].

DiGA Success stories

As of 10 January 2021, a number of ten DiGAs were already approved by BfArM (The DiGA directory—online at <https://diga.bfarm.de/de/verzeichnis>; see Table 2). Out of these ten, three were permanently added to the BfArM direc-

tory, while the rest of seven were temporarily accepted [2]. |

Sources

The list of sources is available on the DGPharMed website www.dgpharmed.de under the menu „JOURNAL > References.“

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