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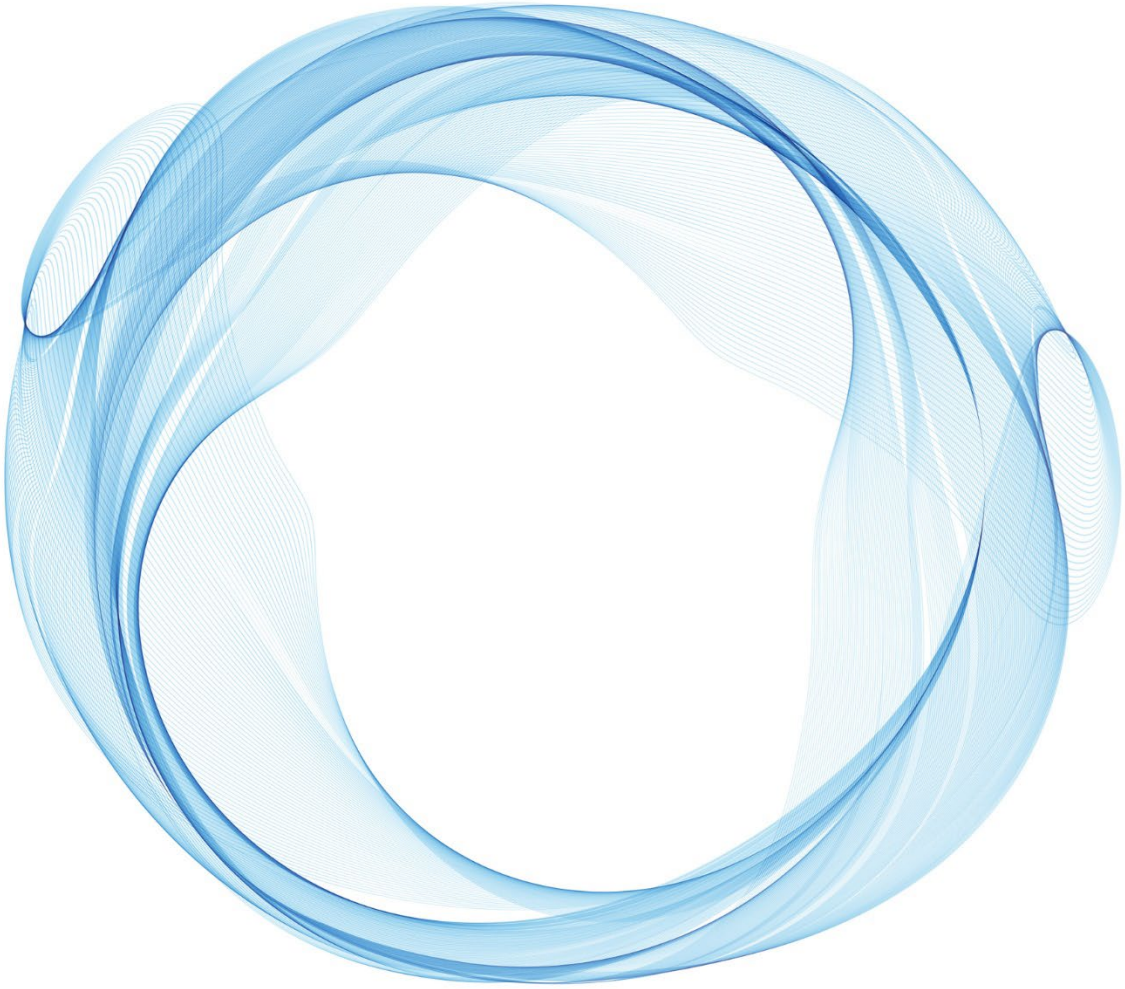


Point of View

A Promising Outlook for Digital Therapeutics (DTx) in Europe – how can biopharma capitalise?

November 2023

Contents

Introduction

The Digital Therapeutics (DTx or PDTs) market has taken large strides in the last few years, growing from infancy to a mature, well-respected older version of its predecessor, with widely developing business models and use-cases available to participate in commercial activities alongside other, more traditional pharmaceutical players. Regulators around the globe are also developing frameworks for research & development, clinical validation, as well as the general regulatory requirements needed for entering the market.[1,2]

Driven by technological developments, healthcare cost pressure and consumer demand for convenience, the Digital Therapeutics (DTx, see below for a detailed overview) funding, has grown significantly over the past few years[3]. Among the three continents – Asia, America and Europe, Europe is currently uniquely positioned to be a leader for DTx clear market access pathways into the public health systems with regulations currently existing in Germany, France and Belgium.

Thanks to the regulatory pathways' development in Europe, the above-mentioned EU markets often act as an attractive market entry point, even for non-EU based companies.

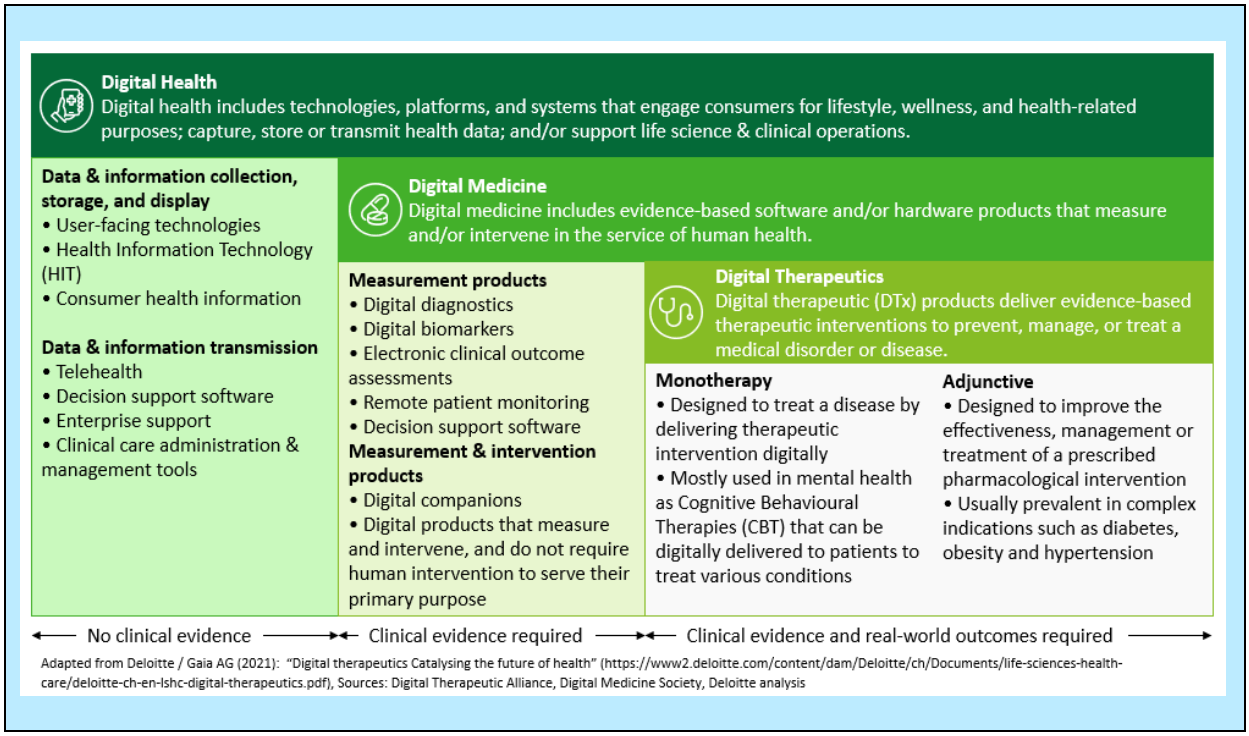
Deep-Dive on DTx: Definition and differentiation with Digital Health and Digital Medicine

Digital Therapeutics (DTx) are evidence-based therapeutic interventions driven by software aimed at preventing, managing, or treating a medical disorder or disease. In other words, DTx are patient-facing software applications that have a demonstrated clinical benefit and assist patients in dealing with all mentioned steps of disease's lifecycle...[4] These solutions can function as standalone therapies or be prescribed in combination with medication, often leading to improved patient adherence. Digital health, digital medicine, and digital therapeutics also offer industry stakeholders an opportunity to craft more personalised experiences and new ways to become patient-centric.

Please note that this product category fundamentally differs from health apps without proven clinical benefit not approved by regulatory bodies for claims of safety, risk and efficacy. Such apps are also never reimbursed by national bodies or payers!

[1] Guidances with Digital Health Content | FDA (2023); URL: https://www.fda.gov/medical-devices/digital-health-center-excellence/guidances-digital-health-content; retrieved on: 25. 10. 2023.
[2] BfArM - Digital Health Applications (DiGA); URL: https://www.bfarm.de/EN/Medical-devices/Tasks/DiGA-and-DiPA/Digital-Health-Applications/_node.html; retrieved on: 25. 10. 2023.
[3] Digital Therapeutics – medical intervention beyond the pill (2022); URL: https://dealroom.co/blog/digital-therapeutics-startups-report-2022; retrieved on 22. 10. 2023.
[4] Digital therapeutics (DTx); URL: https://edps.europa.eu/press-publications/publications/techsonar/digital-therapeutics-dtx_en; retrieved on: 27. 9. 2023.

Fig. 1: Differences between digital health, digital medicine and digital therapeutics



In previous publications in the last years[5], we have taken a global perspective on DTx and its increasing relevance to transforming the Life Sciences and Health Care industry to achieving our Deloitte vision of the Future of Health. In this publication we aim to provide an overview of the strategic market opportunities the European market provides to DTx manufacturers. Additionally, the publication provides in-depth knowledge on the different market regulatory pathways in the appendix for further reading.

The potential of DTx in better healthcare provision and patient outcomes

As described back in 2020[5], today's healthcare systems are confronted with several pressing issues, such as:

- The need to control healthcare costs.
- The increasing incidence and growing prevalence of preventable chronic diseases.
- The need for safe and accessible solutions for the treatment of chronic and mental health diseases.
- The growing focus of suppliers, providers and payers on predictive, preventative, personalised and participatory healthcare for earlier detection of onset of disease and better patient outcomes.
- The increasing shortage in healthcare workforce.

DTx have been identified to help address these issues. It is predicted that the largest impact will be on important stakeholders in the healthcare systems: Patients, Providers, Payers and Policymakers.

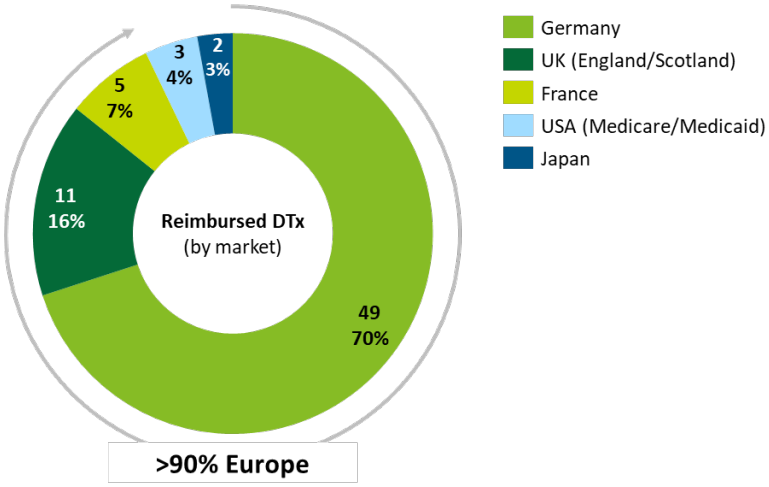
[5] Vanoli et al. (2021): Digital therapeutics - Catalysing the future of health, Deloitte Switzerland; URL: https://www2.deloitte.com/ch/en/pages/life-sciences-and-healthcare/articles/digital-therapeutics.html; retrieved on: 2.4.2023.

One prominent example is mental health. Driven by demographics, socio-economic factors and further accelerated by COVID-19, WHO reported that 1 in 8 people are diagnosed with a mental health condition, which translates to 970 million people globally in 2019[6]. This surging demand is met by a shortage in ambulatory and stationary care, resulting in prolonged waiting times for patients and a higher risk of negative patient outcomes due to delayed access to care. In addition to being easily accessible and generally low-cost, in certain mental health indications, approved DTx showed potential to help improve symptoms, slow the progress of disease, and support traditional treatment by allowing patients to work with a psychotherapist in order to improve their condition between sessions[7,8]. In similar ways, DTx are becoming more integrated into established clinical pathways/disease management programs, such as those for diabetes[9], thus potentially alleviating current issues in the healthcare sector.

In recent years, a lot has changed in terms of DTx regulations, adoption, and usage in Europe. In this report, we not only describe the status quo of DTx in Europe, but we also investigate – what we believe – is a promising future for DTx in Europe and what are best practices for DTx and biopharma companies in creating successful business models in DTx.

It is worth mentioning that Europe is currently in a leading position for DTx reimbursement, which might be surprising given the fact that other markets such as the US and China are of a higher priority to suppliers of medical products.

Fig. 2: Reimbursed DTx comparison by country [10,11]



[6] World Mental Health Report – Transforming mental health for all (2022); URL: https://www.who.int/teams/mental-health-and-substance-use/world-mental-health-report; retrieved on: 15. 9. 2023.
[7] Arjona et al. (2023): Impact of Digital Health Apps Among Patients with Mental Health Issues: An Integrative Review; Canadian Journal of Nursing Informatics, 18(1); retrieved on: 15. 9. 2023.
[8] Seegan et al. (2023): Efficacy of stand-alone digital mental health applications for anxiety and depression: A meta-analysis of randomized controlled trials; Journal of Psychiatric Research Volume 164, August 2023, Pages 171-183; retrieved on: 15. 9. 2023.
[9] DMP for diabetes goes digital (2023); URL: https://www.aerztezeitung.de/Wirtschaft/DMP-fuer-Diabetes-wird-digital-440940.html; retrieved on: 15. 9. 2023.
[10] Global DTx Reimbursement Landscape; URL: https://www.linkedin.com/posts/michaelpace-dtx_dtx-germany-diga-activity-7053699269991489537-yclc?utm_source=share&utm_medium=member_desktop; retrieved on: 30.10.2023.
[11] DiGA Directory; URL: https://diga.bfarm.de/de/verzeichnis; retrieved on: 18. 9. 2023.

State of the Digital Therapeutics industry in Europe

In Europe, 2019 marked a significant milestone for digital therapeutics as they gained traction, with Germany pioneering the first regulatory pathway for DTx in Europe. The DiGA (Digitale Gesundheitsanwendungen) pathway allows for temporary marketing approval while permanent marketing approval is dependent on proof of a positive healthcare effect through clinical evidence data. This was a key element of the strategic plan, created by Germany's Ministry of Health to advance digital healthcare provision. Unsurprisingly, Germany has quickly become a hub for DTx developers and still has the highest number of approved DTx in Europe, with 26 permanently and 23 provisionally listed as of October 2023.[11]

Since then, similar regulatory pathways have been created in Belgium and France. Some countries that are expected to follow very soon include the UK, Spain and Italy. Almost every European country has, to some extent, presented a digital transformation plan with parts focusing on life sciences and healthcare, with implementation planned between 2025-2030. Overall, the current regulations have been successful in bringing numerous DTx products to market, however a lot of experimentation is still taking place in the approval, clinical evidence, pricing, and reimbursement processes across these countries.

Prior experience in Germany has proven that a reimbursement mechanism is a key requirement for DTx developers. Whilst obtaining marketing approval is a significant part of the process, when the reimbursement model is unclear, it is very difficult to establish a business plan and revenue stream. Likewise, individual contracting for smaller subpopulations of insurance holders has proven to be very time consuming and costly.

Fig. 3: DTx Reimbursement Landscape in Europe[2, 12, 13, 14, 15, 16, 17, 18, 19, 20]

	National value assesment framework	Need for clinical evidence on national level	National reimbursement pathway, funding	Time to market / application evaluation
Germany	☑ DiGA process: Standalone DTx evaluated by BfArM; new legislation for inclusion of class III drafted	☑ provisional inclusion: plausible justification of improvement in care based on scientific evaluation permanent inclusion: clinical evidence has to be provided within 12 months of provisional inclusion	☑ centralised funding for all listed DiGA by GKV-SV, DiGA is reimbursed for a median price of 500 euro	3 months for DiGA Fast Track Assessment by BfArM
Belgium	☑ DTx clinical and/or socioeconomic value evaluated through Validation Pyramid by NIHDI	☑ for M3 tier: clinical evidence and socioeconomic added value	☑ centralised funding for tier M3 DTx: M3 light - temporary reimbursement, M3 plus - permanent reimbursement	the standard procedure may not take more than 180 days
France	☑ DTx clinical evidence, economic dossier and technical documentation evaluted by CNEDIMTS	☑ fast track: initial clinical evidence with a plan for additional data generation standard procedure: added evidence of clinical benefit	☑ centralised funding; flat rate reimbursement during the temporary List of Products and Services inclusion; permanent inclusion - pricing around 350 euro	fast track: 60 days for evaluation + 30 days for validation standard procedure: 12 to 24 months
UK	☑ Evidence Standards Framework (ESF) for proving safety, effectivness and economic impact, evaluated by NHS and other local authorities	☑ for Tier 3a and 3b: demonstration of clinical effectivness	☒ decentralised decision; depends on each local Integrated Care System, can be based on ESF	about 9 months to go through Medical Technologies Evaluation Programme in ESF
Spain	☒	☒	☒ decentralised decision; depends on each Autonomous Community	no standard procedure
Italy	☒	☒	☒	N/A
Netherlands	☒	☒	☒ covered by individual health insurers	N/A
Sweden	☒	☒	☒ covered by some private health insurers	N/A

[12] Life Sciences Regulation in Belgium: Overview (2023); URL: Life Sciences Regulation in Belgium: Overview | Practical Law (thomsonreuters.com); retrieved on: 4. 10. 2023.
[13] mHealth Belgium; URL: Belgian platform for medical mobile applications - mHealthBELGIUM; retrieved on: 4. 10. 2023.
[14] Pricing and Reimbursement Laws 2023/ Belgium (2023); URL: Pricing & Reimbursement Laws and Regulations | Belgium | GLI (globallegalinsights.com); retrieved on: 4. 10. 2023.
[15] Price en chargé anticipée numerique (PECAN) (2023); URL: Prise en charge anticipée numérique (PECAN) | G_NIUS (esante.gouv.fr); retrieved on: 6. 10. 2023.
[16] Reimbursement profiles; URL: Reimbursement profiles | G_NIUS (esante.gouv.fr); retrieved on: 6. 10. 2023.
[17] Improving access to digital therapeutics in Europe (2023); URL: improving-access-to-digital-therapeutics-in-europe.pdf (efpia.eu); retrieved on: 6. 10. 2023.
[18] Digital therapeutics alliance; URL: Home - Digital Therapeutics Alliance (dtxalliance.org),; retrieved on: 6. 10. 2023.
[19] Evidence standard framework for (ESF) for digital health companies; URL: Evidence standards framework (ESF) for digital health technologies | Our programmes | What we do | About | NICE, retrieved on: 6. 10. 2023.
[20] Market access pathways for digital health solutions (November 2020); URL: 20062_COCIR_Market_Access_Pathways_Digital_Health.pdf; retrieved on: 8. 10. 2023.

Reasons for optimism

1. Growing demand for Digital Solutions

Healthcare systems are under pressure to control rising healthcare costs, whilst improving patient outcomes though innovative solutions, better access and higher quality of care.

The demand and cost of healthcare provision is projected to rise significantly across all major geographies, driven mostly by an aging population, unhealthy lifestyles and a prevalence of chronic, non-communicable diseases. In parallel, it is projected that the shortages in healthcare workforce, which is already a burden in all aspects of healthcare today, will continue to worsen in the years to come[21,22]. By 2030, the global healthcare sector will need an estimated 80 million additional workers to meet demand in high-income countries; from this number and around 18 million will be needed for low-income countries.[23]

2. Growing acceptance and trust in Digital Solutions

As with all new technologies and solutions, it takes some time from introduction to broad acceptance and application. This is certainly even truer for health-related solutions, as both caregivers and patients need to understand the impact of innovative solutions and develop trust in the safety and efficacy of usage. Since the caregiver is often the most important gatekeeper in the prescription process (90%[24] of DiGA in Germany are prescribed by a physician), companies need to find ways to educate physicians about the digital solutions and their value to patients.

In our report One Year DiGA in Germany[25] we already described that some physicians are very sceptical about the clinical value add of DTx, with notable differences by age group (50% of <44 years and 90% of >44 years being sceptic).

In parallel, companies need to educate patients about DTx, as often they do not even know about their existence and benefits. For example, a recent survey[26] in Germany revealed that 60% of patients have never heard about digital health applications. That number is alarming, especially when taking into account that the survey was done 2.5 years after the first DiGA was approved in late 2020!

[21] Deloitte (2022) Addressing health care's talent emergency; URL: https://www2.deloitte.com/us/en/insights/industry/health-care/healthcare-workforce-shortage-solutions.html; retrieved on: 18. 9. 2023.
[22] Deloitte (2023): Time to change – Sustaining the UK's clinical workforce; URL: https://www2.deloitte.com/content/dam/Deloitte/uk/Documents/life-sciences-health-care/deloitte-uk-time-to-change-report-updated.pdf; retrieved on: 18. 9. 2023.
[23] Deloitte (2023) Global Health Care Outlook; URL: https://www.deloitte.com/global/en/Industries/life-sciences-health-care/analysis/global-health-care-outlook.html; retrieved on: 20. 9. 2023.
[24] AOK DiGA Survey 11.01.2023; URL: https://www.aok.de/pk/cl/fileadmin/user_upload/AOK-NORDWEST/07-Presse/Dokumente/2023/PI-2023-01-11-DIGA-WL.pdf; retrieved: on 10.4.2023.
[25] Deloitte (2021) Ein Jahr DiGA Chancen für gesetzliche Krankenkassen; URL: DiGA_Digitale Gesundheitsanwendungen_Krankenkassen.pdf (deloitte.com); retrieved on: 18. 9. 2023.
[26] Deloitte Consumer Survey August 2023 (publication wip)

3. Better understanding of requirements regarding clinical evidence

Companies and regulators have learned from unsuccessful applications. Both stakeholders now have a clearer understanding of the clinical evidence required for obtaining market authorization, in addition to being able to establish more realistic timelines for generation of this crucial evidence.

Clinically validated digital solutions (both diagnostical and therapeutical) must show results from pilot studies or clinical trials including clinical benefits such as:

- improved clinical state of the patient;
- shorter hospitalisation or relapse states;
- prolonged survival rates;
- empowered patient self-managing his/ her health;
- improved medication management and adherence to therapies;

and/ or structural benefits such as:

- access to the healthcare system;
- providing decision points for precision medicine;
- enhancements of care delivery quality and others[5].

It is essential to note that according to the Medical Device Regulation (MDR), manufacturers are allowed to use not only direct clinical data, such as data from clinical trials, but also indirect clinical data (e.g., generated by an equivalent device) for clinical evaluation. Some companies are beginning to leverage that expertise by developing a broader product portfolio across indications (GAIA, HelloBetter, Selfapy, Kaia and IVPNetworks) based on initial product launches.

4. Market expansion expected to continue

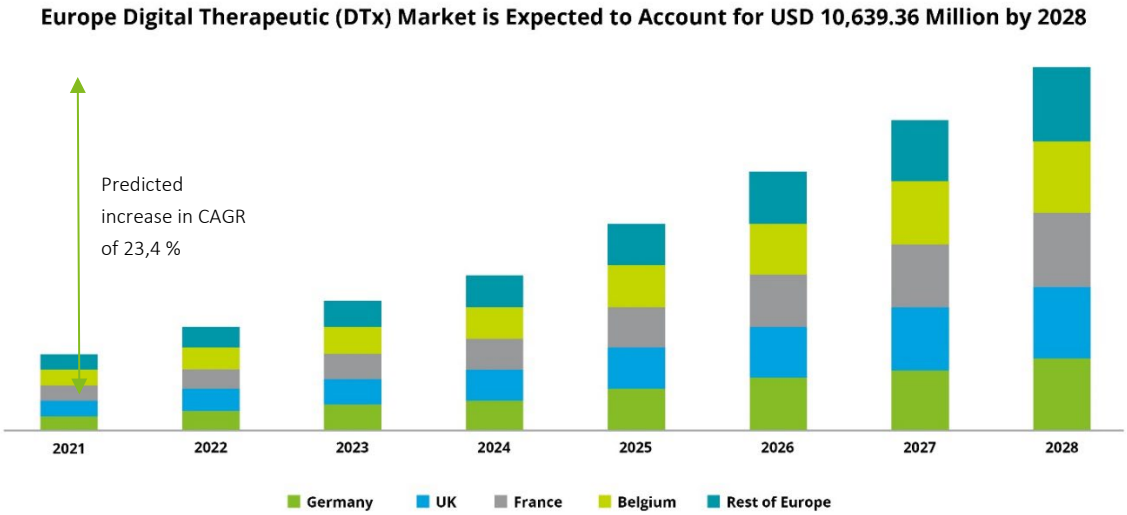
Since Germany implemented the first regulatory pathway for DTx in Europe back in 2019 more countries subsequently started developing a similar framework. Although still an ongoing activity, the European market for DTx, particularly the reimbursed segment, is expected to significantly expand over the next few years.

One of the recently published market research projects expect the DTx market in Europe to triple in the following 5 years to 10.6bn USD[27]. Considering the current market access pathways in Europe, substantial part of this will come from growth in the public reimbursement models.

There are also additional activities from professional pharmaceutical organisations on improving the market access in the EU in general.[28]

[27] Europe Digital Therapeutic (DTx) Market Report – Industry Trends and Forecast to 2028 (2021); URL: https://www.databridgemarketresearch.com/reports/europe-digital-therapeutics-market; retrieved on: 25.10.2023.
[28] Improving access to digital therapeutics in Europe (2023); URL: improving-access-to-digital-therapeutics-in-europe.pdf (efpia.eu); retrieved on: 9. 10. 2023.

Fig. 4: Prediction of European DTx Market by 2028[27]



5. Continued attractiveness for investors despite negative factors

The digital health market has been growing over the years with its importance highlighted during the COVID-19 pandemic. Between 2019 and 2021, digital health funding in the US increased from 14.8bn USD to 29.2bn USD, while the number of deals increased from 413 (2019) to 736 (2021)[29].

However, in late 2022 and especially in 2023, driven by macro-economic head winds (inflation and interest rates increased) and unfavorable events (collapse of Silicon Valley Bank, seizure of Signature Bank), investment levels dropped significantly, almost reaching pre-Covid levels[30]. This is generally a reason for concern, as the development of DTx requires substantial investments.

However, even in difficult times, some important factors may still make DTx an above-average attractive segment for investors:

1. The Covid-19 pandemic accelerated the confluence of many trends in the healthcare sector, most notably consumers' preference for accessibility and convenience. Leading health systems expect the digital transformation for healthcare to become more consumer-friendly while simultaneously changing their operations, culture, and use of technology.[31] This trend will not be reversed but may perhaps slow down slightly, depending on future investment decisions.
2. Based on experience from the past three years, both DTx innovators and investors now can develop much more robust business plans and investment cases, based on new insights regarding development times, clinical evidence, uptake rates, price negotiations and reimbursement decision making.
3. More DTx companies move from no/single approved product companies to platform/portfolio of products companies with substantial revenue streams, making further investments less risky.
4. The reimbursement levels for DTx vary, but these are on average around 250 to 300 EUR per therapy (usually 6 weeks) in Germany, so it represents a significant revenue opportunity.

[29] Q3 2022 digital health funding: The market isn't the same as it was (2022); URL: Q3 2022 digital health funding: The market isn't the same as it was | Rock Health; retrieved on: 20. 9. 2023.
[30] H1 2023 digital health funding: A Brave New (lower funding) World (2023); URL: H1 2023 digital health funding: A Brave New (lower funding) World | Rock Health; retrieved on: 20. 9. 2023.
[31] Schudes et al. (2021): Digital Transformation, Deloitte center for health solutions and The Scotsdale Institute; URL: https://www2.deloitte.com/us/en/insights/industry/health-care/digital-transformation-in-healthcare.html; retrieved on 2. 4. 2023.

Necessity of lessons learned to be translated into best practices

Digital Therapeutics (DTx) are becoming more commonly accepted by patients and doctors and the number of approved DTx applications is on the rise.

However, for DTx companies, it is still a challenge to create sustainable business models, as highlighted by some recent events, such as DTx pioneer Pear Therapeutics filing for chapter 11 bankruptcy in the US, and DiGA companies newsenselab GmbH, Rehappy GmbH and aidhere GmbH filing for bankruptcy in Germany. Main reasons for bankruptcy include the lack of evidence for improving the patients' condition (newsenselab[32], Rehappy[33]) and the problems encompassing reimbursement at a price that allows the company to remain profitable (Pear Therapeutics[34], aidhere[35]).

Even though these events may seem to signal downfall of DTx, it is important to mention that Pear Therapeutics assets auctioned off for $6M after the bankruptcy[36] and in the case of aidhere, just two days after insolvency proceedings had started, an investor took over the obviously promising tech start-up[37]. As a result, we could assume that the problem did not lie within the DTx itself but rather in the business model being used, and it is a prime learning opportunity for all other developers. An example of a potentially interesting approach to resolve the issue around profitability could be transitioning from a prescription-only (Rx) to an over-the-counter (OTC) model such as that implemented by Akili, a leading US digital medicine company that is transitioning to this model in an effort to increase profitability, among other predicted benefits. Akili anticipates that the change will "reduce the reliance on payers and enable the company to grow the business in line with the increasing demand for non-drug cognitive treatments" in addition to raising gross margins.[38]

As the DTx industry is still very young and developing, there is still a lot of uncertainty when creating new DTx solutions. From many discussions with DTx innovators and regulators, we were able to synthesize a list of critical questions that companies need to ask themselves right from the start:

[32] Newsenselab threatens high repayment to health insurance companies (2022); URL: https://www.handelsblatt.com/inside/digital_health/app-auf-rezept-newsenselab-droht-hohe-rueckzahlung-an-krankenkassen/28726716.html; retrieved on 25. 9. 2023.
[33] Another two DiGA removed from the list (2022); URL: https://www.ptaheute.de/aktuelles/2022/11/22/erneut-zwei-diga-aus-verzeichnis-gestrichen; retrieved on: 1. 10. 2023.
[34] Pear Therapeutics Files For Bankruptcy As CEO Blames Shortfalls On Insurers (2023); URL: Pear Therapeutics Files For Bankruptcy As CEO Blames Shortfalls On Insurers (forbes.com); retrieved on: 2. 10. 2023.
[35] Aidhere: DiGA provider is insolvent (2023); URL: https://www.aerzteblatt.de/nachrichten/143574/Aidhere-DiGA-Anbieter-ist-insolvent; retrieved on: 2. 10. 2023.
[36] Pear Therapeutics assets sold for $6M at auction after bankruptcy (2023); URL: https://www.mobihealthnews.com/news/pear-therapeutics-assets-sold-6m-auction-after-bankruptcy, retrieved on: 06.10.2023.
[37] Insolvent weight-loss app: This is how it goes on with a new investor (2023); URL: https://www.abendblatt.de/wirtschaft/article239213259/Insolvente-Abnehm-App-So-geht-es-mit-neuem-Investor-weiter.html, retrieved on: 06.10.2023.
[38] Akili Announces Business Transformation, Focusing on Non-prescription Model (2023); URL: Akili Announces Business Transformation, Focusing on Non-prescription Model | Business Wire; retrieved on: 9. 10. 2023.

Development:

- What is the unmet need?
- What clinical evidence is needed?
- Who would pay to generate the evidence?
- What part of the patient population to target?
- How to define outcomes – clinical improvements or system efficiency?
- How many incumbent DTx are already marketed/ how to differentiate?

Reimbursement and Pricing:

- What margins should we expect?
- What to charge for – fee-for-app, fee for subscription, fee for usage, fee for care-package, fee for outcomes?
- How to set the price?
- How to get reimbursed in public systems?
- How to educate prescribers about clinical value added?
- Possibility for integration into clinical pathways (Leitlinien)?

Scaling:

- Platform for expansion into other conditions?
- Is the solution transferable to other markets?
- How to market – traditionally (sales force) or digitally?
- Can patient organisations help?

Although they are generally under less financial pressure compared with the typical DTx Start-up, the same set of questions still applies to the life sciences industry when considering the development of digital solutions internally.

Biopharma companies and their pursue of DTx

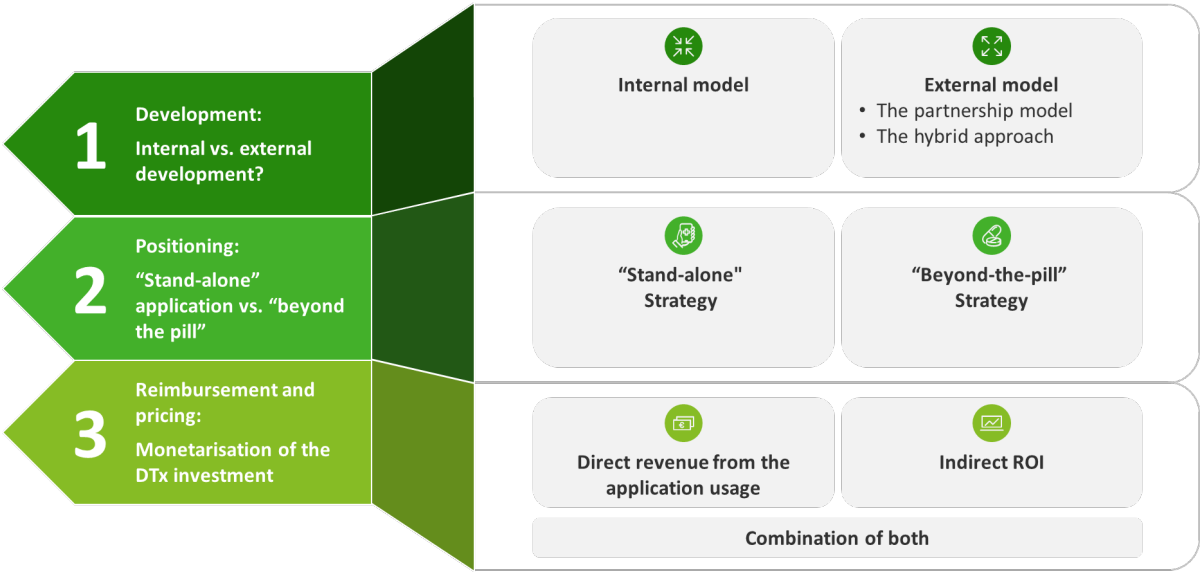
Aside from DTx companies, life sciences companies (Bioharma and Medtech) are also looking to develop DTx to offer a broader range of therapeutic solutions, as such complementing the "traditional" portfolio of drugs and vaccines. Biopharma leaders have acknowledged multiple times, that customers increasingly demand more personalised therapies, which in turn requires real world evidence data from patients to identify subpopulations and other patterns that can then feed back into the development process of personalised treatments. This is not predicted to be a disruptive change but will happen incrementally over time. However, biopharma companies are well advised to start exploring the potential of DTx now, to build capabilities and talent to be competitive in the future.

Is there a risk for biopharma in just ignoring the DTx and continue doing business as usual? There are indeed some risks for biopharma companies, included but not limited to: lack of access to quality real world data to develop more personalised treatments; more difficult value proof in pricing and reimbursement negotiations; more difficult differentiation to competitor offerings; greater distance from patients – lack of customer-centricity and deep insights into patient journey.

Some strategic considerations for biopharma DTx investments

Many biopharma companies already invested into DTx, but for very different reasons. As such, each biopharma company needs to answer a set of questions to identify how to best capitalise from a DTx investment.

Fig. 5: Strategic decisions for DTx development



a. Stand-alone" application vs. "beyond the pill"

A major strategic question to answer is whether to create a "stand-alone" application vs. a "beyond the pill" approach where a medication and an application are combined to create additional benefit and/or differentiation in highly competitive markets. This very often depends on the business case and is closely linked to the next question below.

b. Monetarisation of the DTx investment

Another important consideration is the monetarisation of the DTx investment. Whereas with a "beyond the pill" approach, very often the ROI is expected to materialise in more medical product revenue, in the case of stand-alone applications there are a variety of monetarisation opportunities to consider:

1. Direct revenue from the application usage, either through reimbursement pathways, or out of pocket where such pathways may not exist. Revenue will be low compared to other products in a biopharma company's pipeline, however there may be indirect benefits from building new stakeholder relationships, new digital capabilities, and consumer perception.
2. Indirect ROI, where biopharma companies are mainly interested in generating real world evidence data that than can be used in the development of more personalised treatments or in the design of clinical studies. This approach has the potential to significantly disrupt the traditional R&D process in some areas and to create high ROI in the future.
3. This can also be a mix of both, depending on the strategic objectives.

c. Internal vs. external development

The next decision very often revolves around whether to develop an application internally or partner with DTx manufacturers. Today, biopharma companies are experimenting with a lot of different approaches, but these models, some more often used than others, can be identified as the following:

I. The internal model

Gives biopharma companies more control over the product and marketing strategy, while often requiring a longer ramp-up period due to the need to build DTx development expertise and resources from scratch such as:

- Software development (a biopharma company is not a software house),
- Clinical effectiveness proof (clinical trials of DTx might require experiences with digital data solutions),
- Regulatory expertise (biopharma is often not the expert in medical device regulations),
- Market access and reimbursement expertise (in some countries, specific innovative pathways are in place).

Example: Sanofi's digital accelerator

The Accelerator will develop products and solutions that will support Sanofi's mission to transform the practice of medicine with the use of digital, data and artificial intelligence (AI). Based in Paris, it already brings together a team of over 75 experts from around the world and will continue to recruit top talent in digital product management, full stack development, and data science[39].

II. The partnership model

Might expedite the time to market but biopharma companies need to compromise on the application features (e.g., user interface), clinical data and pricing.

Partnerships are created for various reasons, such as:

1. Co-development (cost sharing), e.g., in December 2022, Boehringer Ingelheim and Click Therapeutics announced an expansion of their funding support to develop a new prescription DTx supporting patients with schizophrenia.[40]

[39] Sanofi Press release (2022); URL: Sanofi launches its first Digital Accelerator fueled by new talent and focused on growth; retrieved on 6. 10. 2023.
[40] Boehringer Ingelheim and Click Therapeutics expand their existing Collaboration to develop Prescription Digital Therapeutics for Schizophrenia (2022); URL: New digital Tx collab with Click | Boehringer Ingelheim (boehringer-ingelheim.com), retrieved on: 5.6.2023.

2. Distribution (revenue sharing), e.g., Deprexis, an online program manufactured by GAIA AG, offers effective therapy support for patients with depression and is globally licensed to Servier Deutschland (except for the US and Japan) for distribution.[41]
3. Knowledge transfer, e.g., Takeda launched CDPATH™ program with a goal to support clinicians and patients with Crohn's disease in making informed decisions and creating a personalised disease management plan. Takeda partnered with MiTest Health and Prometheus Laboratories Inc.

The relationship must be beneficial for both sides – biopharma companies lack some of the development skills, while DTx companies may lack funds and marketing power. That is where the biopharma industry can step in and leverage their respective strengths regarding marketing and access to prescribers in a partnership model. The depth of the partnership is very individual and must support the overall company strategy.

III. The hybrid approach

Is a combination of partnerships with internal capability build to ideally get the best of both worlds.

Example: Bayer announced a hybrid approach to DTx:

On May 31st 2023, Bayer created a new business unit in its global consumer health division, which focuses on digital and digital-supported consumer health opportunities. The group will focus on addressing unmet needs in its core categories, delivering new evidence-based precision health products to market that offer end-to-end self-care, as well as scaling technologies globally. It will work with start-ups and other digital health providers as well as advance Bayer's existing digital capabilities[42].

Biopharma companies need to assess their own capabilities very carefully and must acknowledge that DTx development requires a significantly different skillsets compared to drug development. Major considerations include the time and cost to build internal capabilities, which includes attracting the right talent vs. compromising on control regarding product features, user experience, ownership of data when partnering with a DTx developer.

Key success factor – mastering the regulatory complexity

DTx legislation is currently fragmented among European countries, therefore it is important to choose the best market access points. National regulatory differences lead to variations in which documents are submitted, which in return affects the amount of time spent preparing such documents. This has a direct impact on the evaluation time and key decisions, such as whether to follow fast-track versus standard procedures, reimbursement rates and even the likelihood of receiving reimbursement for the digital solution at all.

Additionally, in some markets, there are different ways to get DTx reimbursed. For example, in Germany, selective contracting with single payers may seem to be the fastest way to market, but this will only provide reimbursement for a smaller group of publicly insured patients. The DiGA pathway may take more time, but ultimately this will make DTx eligible for reimbursement for all publicly insured patients.

Biopharma companies are very experienced in accessing the healthcare markets with their core medicinal products. There are however major differences in bringing digital therapeutics and diagnostics to the same markets. If the pharmaceutical industry desires to bring clinically validated solutions to market, the unique national market access pathways must be fully understood.

[41] Depression therapy; URL: Online Therapy Program | Servier Germany, retrieved on: 5.6.2023.
[42] Bayer Press release (2023): Bayer launches unit to develop new precision health consumer products, retrieved on: 6. 10. 2023.

Even though there are growing expectations for having the digital health market properly regulated and synchronised, the regulatory framework based on the Medical Devices Regulation (MDR) doesn't fully cover all the challenges regarding the adoption of digital solutions.[43] The simplest description of the current situation is "fragmented but on its way to harmonisation", with success of German DiGA being one of the drivers and inspiration.

Future evolution of the DTx reimbursement model in Europe

Even though Europe is clearly leading the peloton of standardised market access opportunities for digital health solutions, a pan-European approach to the evaluation of these solutions that would facilitate such processes between different countries remains a challenge. The current study of EU agency supporting health innovations[44] pointed out several strategic recommendations which should be considered to enable DTx acceleration in Europe. Some of the most important recommendations include:

- MDR and CE mark are insufficient as a framework for developing reliable digital health innovations; more focus is needed on DTx in the Health Technology Assessment guidelines. Life science companies are experienced in HTA application for medications, thus a move in this direction may better support further life-science companies' engagement.
- Interoperability, data safety and trustworthy data processing are crucial. European Health Data Space, ePA (Elektronische Patientenakte) & eRezept in Germany or PS (Pacientsky souhrn) & eRecept (electronic prescription) in Czechia are examples of correct approaches in the space of regulatory development.
- EU needs a vision for a common DTx single market and must take steps toward harmonising national approaches in this field. If the rules are compatible, this creates a much bigger opportunity for large multinational life science companies to buy in to DTx.
- There is a visible need to create a network of innovation centers in leading university hospitals that support co-developing, consulting, testing and validating digital health innovations.[45] Leveraging existing KOL networks that life-science companies have experienced collaborating with is important to further grow the value of clinical development in digital health clinical.

In the short-term, increased complexity is to be anticipated as more countries continue to adopt regulatory frameworks for DTx. However, in the long-term, an EU-wide harmonisation could significantly accelerate DTx business models by cutting down on time-to-market and development cost by avoiding duplication.

[43] Virkkunen et al. (2022): Single market for digital therapeutics; URL: https://www.europarl.europa.eu/doceo/document/P-9-2022-003581_EN.html, retrieved on: 2.5.2023.
[44] EIT_Health_DiGA_report (eithealth.eu), retrieved on: 25.10.2023.
[45] Olesch et al. (2023): Towards harmonised EU Landscape for Digital Health: Summary of the roundtable discussions in selected EIT Health InnoStars countries; URL: https://eithealth.eu/wp-content/uploads/2023/02/EIT_Health_DiGA_report_Jan2023.pdf, retrieved on: 2.5.2023.

Conclusions

DTx market globally is growing and creates new opportunities for all stakeholders – patients, payers and providers and is still better overseen by the regulators that support the inclusion of DTx solutions into health systems. Europe is playing a key role in bringing the solutions to the health systems with paving the way for public reimbursement. DiGA program in Germany is despite many challenges in pricing and clinical validation becoming the model for other countries to follow.

It should be expected that DTx will fit even more into the business model of pharma companies as standalone, drug companion or decision support solutions to improve patient treatment compliance and disease insides while new targeted therapies with higher risk profiles will be developed under the strict pharma rules[46].

Pharmaceutical companies are already invested in the DTx market and the business models for best fit with the digital solutions are rapidly developing. Consideration of partnerships, internal development or consortiums need are important from the start. Furthermore, regional and therapeutical areas considerations are crucial for successful market access. And finally, current operational or organisational setup of pharmaceutical companies often does not support to the best possible extent development and further utilisation of DTx solutions within the pharma space.

[46] Using digital solutions for treatment of burns – Artificial intelligence in the management and treatment of burns: a systematic review – PMC (nih.gov) retrieved by: 25.10.2023.

Country deep dive – pioneers

GERMANY

Germany is generally recognised as a DTx reimbursement framework pioneer with an active fast-track model, which has been an inspiration for other European countries, such as France and Belgium.

DiGA

The Digital Healthcare Act (DVG) was passed in December 2019, and it stipulates reimbursement criteria for patient-oriented digital health applications (DiGAs) that are Medical Devices of low risk (must be classified as a class I or IIa medical device according to Regulation (EU) 2017/745 on medical devices or according to Directive 93/42/EEC). As of October 2023, there are 49 DTx (with 23 being included provisionally, 26 being permanently recorded) being reimbursed. Based on this framework, the key factor for market access in Germany (similarly to France and Switzerland) are clinical data, in contrast to e.g. Spain and Italy, where decisions are based more on budgetary impact data (economic benefits).

In order to be reimbursed by the statutory health insurance payers, the DTx must be included in the DiGA Directory. It confirms successful evaluation of safety, functionality, quality of the application, data protection, data safety, interoperability with existing health IT infrastructure and positive care effect which is performed by the regulator – BfARM.

In addition, from January 2024 the manufacturer will have to provide evidence of compliance with security requirements for digital health applications known under the abbreviation BSI TR-03161, created under the Technical Directive by Federal Office for Information Security (BSI).

If the manufacturer meets the safety, functionality, quality, data protection, interoperability, and data security requirements, the DTx solution may be preliminarily admitted for 12 months with plausible justification of improvement in care based on scientific evaluation concept prepared by a manufacturer-independent institution. After the trial period of 12 months, the study results must be submitted (with extension to 24 months being the option). The BfArM examines these and subsequently grants a permanent listing in the DiGA Registry, no longer than 15 months after first listing.[47,48,49]

During the first year, the price is determined by the manufacturer, and usually falls within the maximal reimbursement prices for groups or similar DiGAs. After inclusion into the DiGA Registry, a price negotiation takes place between the manufacturer and the National Association of Statutory Health Insurance Funds (GKV-Spitzenverband) during the first year/trial period. The negotiations mainly consider outcomes-based components such as use, patient-reported experience measures, patient-reported outcome measures, etc. The negotiated reimbursement, usually significantly lower, replaces that set by the manufacturer during the 13th month and is valid for 12 months. To enable reimbursement of additional time spent by physicians in relation to the DiGA prescription and management, the D'GA's manufacturer should specify the medical services that are necessary for its use.[47]

Despite the increase in the number of prescriptions, DiGA is still not yet widely used. Only a small subset of German medical professionals (approx. 4% of about 180,000 doctors) issued prescriptions for DiGA. Doctors are the key players in the spread of DiGA; in terms of patient access, they hold a privileged position as they prescribe digital applications and can significantly influence and monitor patient compliance.[50] So far, the

[47] BfArm (2023): Digital Health Application (DiGA); URL: https://www.bfarm.de/DE/Medizinprodukte/Aufgaben/DiGA-und-DiPA/DiGA/_node.html, retrieved on: 9.5.2023.
[48] MedTech Europe (2021): Recognising the value of digital health apps: An assessment of five European healthcare systems; URL: https://www.medtecheurope.org/wp-content/uploads/2021/11/2111_v4.8_mte_dht_reimbursement16.11.2021-2.pdf; retrieved on: 11.5.2023.
[49] Gensorowsky et al. (2022): Market access and value-based pricing of digital health applications in Germany; URL: https://resource-allocation.biomedcentral.com/articles/10.1186/s12962-022-00359-y; retrieved on: 11.5.2023.
[50] Dahlhausen et al. (2022): There's an app for that, but nobody's using it: Insights on improving patient access and adherence to digital therapeutics in Germany; URL: https://journals.sagepub.com/doi/full/10.1177/20552076221104672; retrieved on 10. 10. 2022.

majority of all DiGA (about 55 %) have been prescribed by only three groups of physicians – general practitioners, otolaryngologists and orthopedic surgeons.[51] The future of the framework could lie in scope expansion to DiGAs with higher class (IIb and III) or to non-patient facing digital health solutions, such as clinical decision support tools[52], since currently DTx approved under DVG cannot be used exclusively by healthcare providers and professionals.

DiPA

DiPAs should counteract the growing challenges of long-term care and general care in the outpatient sector. Through the Digital Care and Care Modernization Act (DVPMG, 2021), DiPA are anchored as a regular component in the catalog of benefits of social long-term care insurance. Three main objectives are pursued:

- The reduction of the impairment of self-employment, or
- Counteracting an aggravation of the need for long-term care, or
- Stabilization of the home care situation of those in need of care by supporting relatives or other caregivers.[53]

The seven benefit areas of impairment include mobility, cognitive and communicative skills, behaviors and psychological problems, housekeeping and the organisation of everyday life as well as social contacts. The use of DiPA is also intended to improve communication with family caregivers and nursing staff. Accordingly, the focus is on two target groups - persons in need of care, and relatives or other voluntary caregivers.[54]

A DiPA can but does not have to be a medical devi–e - if it is a medical device, the nursing application must correspond to the low-risk class (I or IIa). In addition to the software, DiPA can also contain hardware (e.g., devices, sensors). An application towards the regulator (BfArM) with CE certification can be listed as DiPA and as DiGA.[55,56]

Analogous to the DiGA, DiPA:

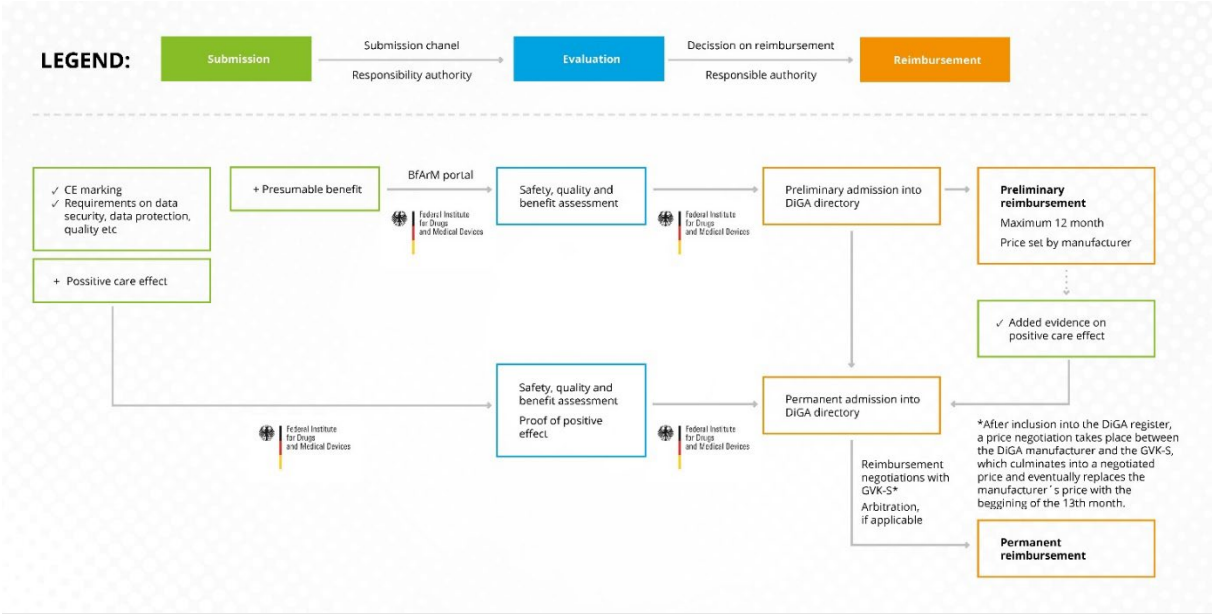
- offers counselling services,
- introduces a similar test procedure, but does not provide for a trial period, so that the nursing benefit must be proven within three months when the application is submitted, and
- establishes a DiPA directory of the BfArM according to § 78a Abs. 3 SGB XI.

The conclusion of the short price negotiation takes place at DiPA within three months of inclusion in the DiPA directory between GKV-SV (in agreement with the BAGüS) and DiPA manufacturers – the remuneration agreements are generally arbitrable.[57] In the first year of approval, there will therefore be no freely determined manufacturer prices for DiPA.

[51] TK (2022): DiGA-Report2022; URL: https://www.tk.de/resource/blob/2125136/dd3d3dbafcfaef0984dcf8576b1d7713/tk-diga-report-2022-data.pdf; retrieved on: 25. 11. 2022.
[52] MedTech Europe (2021): Recognising the value of digital health apps: An assessment of five European healthcare systems; URL: https://www.medtecheurope.org/wp-content/uploads/2021/11/2111_v4.8_mte_dht_reimbursement16.11.2021-2.pdf, retrieved on: 11.5.2023.
[53] BfArM Lectures (2022): BfArM in dialogue: DiPA – Characteristics of a DiPA; URL: https://www.bfarm.de/DE/Aktuelles/Veranstaltungen/Termine/2022-10-26-dialog-dipa.html?nn=1261776; retrieved 6. 11. 2022.
[54] BfArM Lectures (2022): What is a digital care application (DiPA)?; URL: https://www.bfarm.de/DE/Medizinprodukte/Aufgaben/DiGA-und-DiPA/DiPA/_node.html; retrieved on: 6. 11. 2022.
[55] Federal Office of Justice (2022): § 40a Abs. 1 b SGB XI; URL: https://www.gesetze-im-internet.de/sgb_11/__40a.html; retrieved on 14. 11. 2022.
[56] BfARM Lectures (2022): DiPA - Legal basis of SGB XI and DiPA-Decree; URL: https://www.bfarm.de/DE/Aktuelles/Veranstaltungen/Termine/2022-10-26-dialog-dipa.html?nn=1261776; retrieved on: 14. 11. 2022.
[57] Bundesarbeitsgemeinschaft der supra-lokale Träger der Sozialhilfe und der Einintegrationhilfe

The person in need of care will have to apply for the eligible care claim at the respective payer (approval required), so it is not a classic prescription. Billing is carried out directly between the insured person and the DiPA manufacturer. The benefit entitlement for the use of digital care applications is limited to a maximum of EUR 50 per month (per insured person, not per application) - additional costs must be borne by the persons in need of care themselves.[58] This maximum amount also includes the remuneration of supplementary support services.

Fig. 6: Reimbursement pathway in Germany



FRANCE

French president recently declared that there would be increased focus on digital health solutions and intention to learn from experiences and mistakes made during the first few years of DiGA in Germany. The Prise en Charge Anticipée "PEC-AN", which includes a fast-track component, has been implemented as a result.

PEC-AN (Fast-track reimbursement)

Various agencies, including National Digital Agency (ANS), the French National Authority for Health (HAS) and the National Agency for the Safety of Medicines and Health Products (ANSM) are helping manufacturers by developing guidelines on digital health solutions development and the reimbursement pathways. In comparison to DiGA, the system is intended not only for class I or IIa devices, but also for class IIb devices.

There are several ways to get a solution reimbursed in France.[59] The Fast-track reimbursement pathway allows quick market access and quick access to patients (PEC-AN).[60] The system is meant for digital therapeutics or remote patient monitoring solutions that are innovative and yet sufficiently mature.

In order to be considered for PEC-AN, a manufacturer must submit:

- a technical certification for cybersecurity, interoperability and GDPR (also called proof of compliance),
- CE marking,
- initial clinical evidence in form of medico-technical dossier with a plan for additional data generation and economic dossier with initial price request to ANS, respectively Medical Device and Health Technology Evaluation Committee (CNEDiMTS).

[58] Federal Office of Justice (2022): § 40b SGB XI Entitlement to benefits during use DiPA; URL: https://www.gesetze-im-internet.de/sgb_3/__40.html; retrieved on: 7. 11. 2022.
[59] G_NIUS (2023): Types of "reimbursement" financing; URL: https://gnius.esante.gouv.fr/en/financing/reimbursement-profiles; retrieved on: 9. 5. 2023.
[60] G_NIUS (2023): Prise en Charge Anticipée – PECAN; URL: https://gnius.esante.gouv.fr/fr/financements/fiches-remboursement/prise-en-charge-anticipee-numerique-pecan; retrieved on: 9. 5. 2023.

Once approval is received from the CNEDiMTS based on the first available data and from the ANS on compliance with interoperability and security standards, the solution is reimbursed for a non-renewable period of one year with a flat rate payment.[61] This model allows companies to further explore and finalise the clinical benefit study while being already reimbursed, with the goal to become reimbursable under the standard system after the defined trial period.

From the start of digital early reimbursement, the company must file a request for standard reimbursement with added evidence of clinical benefit (for DTx) or at least an improvement on how care is organised (for remote monitoring activity):

- within 6 months for therapeutic digital solutions (LPP pathway)
- within 9 months for remote monitoring activities (LATM pathway)

The medico-economic dossier is submitted to The Economic and Public Health Committee (CEESP) only if DTx claims class I, II or III in added clinical value and is likely to have a significant impact on the French health insurance scheme expenditures. CNEDiMTS evaluates actual clinical benefit and clinical added value while CEESP formulates pharmaco-economic evaluation.

Additionally, France has several other pathways to promote innovation through funding, such as the Innovation package for Medical Device Manufacturer, Article 51 LFSS 2018 and Institution's own funds.[59]

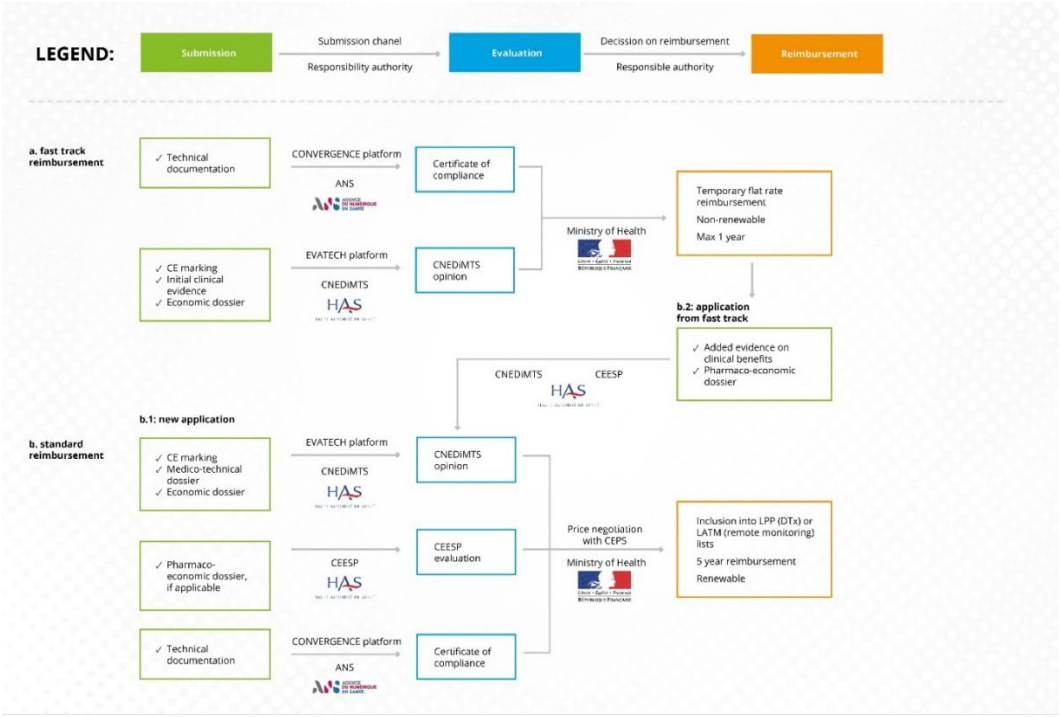
Article 51 (Temporary funding mechanism)

Article 51 encourages, supports, and accelerates the deployment of innovative experimental health organisations based on new financing methods that depart from many of the healthcare system's standard rules. This reimbursement is funded either through the Fund for Innovation in the Health System or via the Regional Intervention Fund, which covers the start-up and engineering credits for Article 51 regional projects.[62] The Innovation Package is a temporary funding mechanism for a technology, contingent on carrying out a study to provide clinical or cost-effectiveness data to prove its efficacy and usefulness.[63]

In addition, when a medical device is not financed directly through the patient's hospitalisation, healthcare facilities can choose to finance them from their own funds and not through payer reimbursement.[64]

[61] healthxl (2023): The 101 on the New French Reimbursement Pathway; URL: https://www.healthxl.com/blog/the-101-on-the-new-french-reimbursement-pathway; retrieved on: 9. 5. 2023.
[62] G_NIUS (2023): Article 51 LFSS 2018; URL: https://gnius.esante.gouv.fr/en/financing/reimbursement-profiles/article-51-lfss-2018; retrieved on: 9. 5. 2023.
[63] G_NIUS (2023): Innovation Package; URL: https://gnius.esante.gouv.fr/en/financing/reimbursement-profiles/innovation-package; retrieved on: 9. 5. 2023.
[64] G_NIUS (2023): Institution's own funds; URL: https://gnius.esante.gouv.fr/en/financing/reimbursement-profiles/institutions-own-funds; retrieved on: 9. 5. 2023.

Fig. 7: Reimbursement pathway in France



BELGIUM

One mid-size European country with a clear focus on digital therapeutics reimbursement and early adoption is Belgium. It may be a good country to consider making a first step into the digital world for pharma, particularly because the market is smaller and can allow for rectification of mistakes in an easier manner than in major markets such as Germany and France.

In late January 2021, the National Institute for Health and Disability Insurance (NIHDI) announced that the Insurance Committee had given the go-ahead for medical reimbursement of medical applications (mobile health applications or mHealth applications). Any manufacturers with ambitions to have digital therapeutics approved for reimbursement which goes through an approval process to reach the top of Belgium's mHealth "pyramid", can now get their app reimbursed by NIHDI.[65] In Belgium, several mobile applications are currently being used at every stage of the patient journey; from prevention and diagnosis to treatment and follow-up. In addition, they can also play a role in online medical education.

mHealth Belgium

The mHealth Belgium is the platform for mobile applications that are CE-marked as a medical device. It works closely with three national authorities – FAMHP, NIHDI and the eHealth Platform.

The FAMHP (Federal Agency for Medicines and Health Products) is the competent authority for all things related to the quality, safety and efficacy of medicines and health products, including medical devices. It is responsible for level M1 products within mHealthBelgium.[44] M1-level devices must have:

- CE marking as an approved medical device, and it is a general indication of its safety and quality.

[65] Brown (2021): Digital Therapeutics Regulation: 3 Leading Countries (inc. FDA, MDR, & DiGA); URL: https://www.smartpatient.eu/blog/fda-mdr-digital-therapeutics-regulation-leading-countries; retrieved on: 11.4.2023.

The eHealth Platform is a federal government institution with the mission to promote and support the providing of a well-organised, mutual electronic service and exchange of data between all healthcare stakeholders, with safeguards in the areas of data security, the privacy of the patient and the caregiver, as well as respecting medical professional confidentiality. It oversees level M2 products within mHealth Belgium. Solutions in M2-level need to meet requirements regarding:

- data privacy,
- authentication,
- identification,
- therapeutic relationship,
- informed consent in addition to all M1-level requirements.

The National Institute for Health and Disability Insurance (NIHDI) is responsible for the reimbursement of medicines, medical devices and medical provisions. It is in control of validation of level M3 within mHealth Belgium's validation pyramid. This third and highest level of this validation pyramid is now also available, and it regulates the funding of mHealth applications. Applications which fulfil the M3 level requirements can receive full reimbursement in Belgium.[66]

To pass the M3 level, the manufacturer must submit:

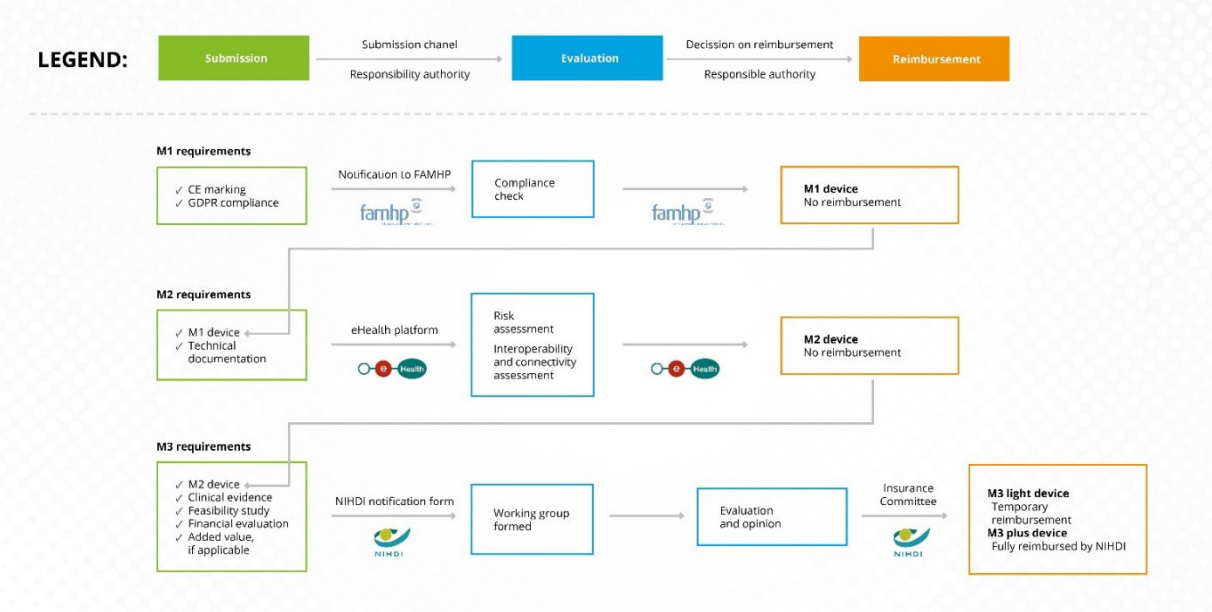
- a dossier showing the clinical and/or socio-economic benefits which demonstrate that the DTx brings clear value into a specific care path.

In the case that specific care path reimbursement has not been previously modified for the integration of DTx, the NIHDI restructures the financing of that pathway accordingly. This establishes requirements for DTx to be included in scope and thus to be reimbursable. DTx that have completed levels M1 and M2 of the validation pyramid and meet the criteria for mobile medical applications within a specific care process can indicate this via self-certification in the portal.[67]

Once a List of reimbursable devices meeting the criteria for reimbursement is published by NIHDI, the manufacturer will have to apply to be included on this list to receive reimbursement. Only after registration on the NIHDI list will the company be able to register as an M3. To have an application integrated within the health and reimbursement system, one must submit a notification form to the NIHDI. After submission, a working group (independent medical experts, representatives of the patient organisation, etc.) is formed to evaluate if the application is fit for M3 level and reimbursement. The working group also proposes a recommendation to the Insurance Committee of NIHDI. The insurance committee will then decide whether to move forward with the integration of the DTx into the healthcare and the reimbursement systems. If the integration and reimbursement is temporary, it will be displayed as 'M3 light'. When the use of mobile medical applications has been definitively integrated in the financing of the care process, it is referred to as 'M3 plus'.[48, 67, 68, 69]

[66] mHealthBelgium (2022): Validation pyramid; URL: https://mhealthbelgium.be/validation-pyramid; retrieved on: 12.4.2023.
[67] mHealthBelgium (2022): Financing; URL: https://mhealthbelgium.be/financing; retrieved on: 12.4.2023.
[68] Osborne Clarke (2021): Breakthrough for digital healthcare in Belgium as scheme launches to reimburse mobile health apps; URL: https://www.osborneclarke.com/insights/breakthrough-digital-healthcare-belgium-scheme-launches-reimburse-mobile-health-apps; retrieved on: 12.5.2023.
[69] INAMI (2022): Possibilité d'intégrer vos applications au système de santé et de remboursement; URL: https://www.inami.fgov.be/fr/professionnels/sante/fournisseurs-implants/Pages/fabricants-distributeurs-applications-mobiles-medicales-notifiez.aspx; retrieved on: 12.5.2023.

Fig. 9: Reimbursement pathway in Belgium



Country deep dive – followers

There are many countries in Europe that are trying to learn from the experiences of the pioneers, in order adjust and customize and create a local solution. Moreover, the health technology assessment regulation, which is anticipated to become a requirement to accessing the medical devices market (which DTx are a part of) in the EU within the next two years, may help to standardise the market.

Examples of two additional major European economies that are developing the market access for DTx solutions are the United Kingdom and Spain.

UNITED KINGDOM

The UK is one of the other few countries with a somewhat standardised pathway for DTx (called digital health technology, or DHT in the UK legislation) assessment and financing through Public Insurance Coverage, however a robust and direct access to statutory reimbursement is still missing.[70]

In contrary to the previously mentioned countries, the pathway for receiving reimbursement in the UK is neither centralised nor national. It is a decentralised regional process with the decision making carried out by the Integrated Care Systems (ICSs), which is a partnership of organisations that come together to plan and deliver joint healthcare services, and to improve the lives of people who live and work in their area.[71,72] DHT can be evaluated by ICSs only after presenting necessary regulatory approvals such as a CE mark and/or a UKCA mark, GDPR UK compliance, Digital Technology Assessment Criteria (DTAC) requirements and registration with the Medicines and Healthcare products Regulatory Agency (MHRA).

To support commissioners in their decision-making, the National Institute for Health and Care Excellence (NICE) has developed a risk-based evidence standards framework.[73] The Evidence Standards Framework (ESF) was developed for evaluating:

- safety,
- effectiveness,
- economic impact of digital health technologies, in the NHS.[74]

However, meeting the ESF standard is currently not connected to any particular reimbursement system. Presently, there is no publicly funded provision of apps available directly for patients. Patients must therefore either self-fund or use apps that are free of charge.[75]

A significant progress in reimbursement of DTx in the UK came with the first positive NICE appraisal for the application Sleepio. In May 2022, NICE announced new guidance that recommends the use of Big Health's Sleepio for the treatment of insomnia, with the app being reimbursed at cost of £45 per patient on the NHS.[76] This is the first DTx in the UK with NICE appraisal, which may lead towards more secure NHS financing for digital health apps.

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[70] Tokarska (2022): What does it take to secure access to digital health apps in the UK?; URL: https://remapconsulting.com/digital-health/what-does-it-take-to-secure-access-to-digital-health-apps-in-the-uk/; retrieved on: 11.4.2023.
[71] Stevovic and Galiazzo (2022): Digital Therapeutics (DTx): how to get reimbursed in the EU, UK and US. An overview of the existing regulatory frameworks; URL: https://blog.chino.io/dtx-how-to-get-reimbursed-in-the-eu-uk-and-the-us-an-overview-of-the-existing-regulatory-frameworks/; retrieved on: 11.4.2023.
[72] NHS England (2022): What are integrated care systems?; URL: https://www.england.nhs.uk/integratedcare/what-is-integrated-care/; retrieved on: 11.4.2023.
[73] Remap (2022): https://www.england.nhs.uk/integratedcare/what-is-integrated-care/; URL: https://remapconsulting.com/digital-health/how-was-the-first-digital-therapeutic-sleepio-assessed-by-nice/; retrieved on: 11.4.2023.
[74] NICE: Evidence standards framework (ESF) for digital health technologies; URL: https://www.nice.org.uk/about/what-we-do/our-programmes/evidence-standards-framework-for-digital-health-technologies; retrieved on: 12.4.2023.
[75] Mason and Larsen (2020): Digital Health Apps and Telemedicine in England and Wales; URL: https://cms.law/en/int/expert-guides/cms-expert-guide-to-digital-health-apps-and-telemedicine/england-and-wales; retrieved on: 13.4.2023.
[76] Pharmaceutical Technology (2022): NICE recommends use of digital therapeutic for insomnia; URL: https://www.pharmaceutical-technology.com/comment/nice-digital-therapeutic-insomnia/; retrieved on: 14.4.2023.

Another advancement was the introduction of the Early Value Assessment (EVA), a process aimed at evaluating promising medical technologies, identifying evidence gaps, and recommending their early adoption in the NHS while continuing to gather further evidence.[77] Currently, there have been eight digitally enabled therapies to treat depression and anxiety in adults conditionally recommended by NICE.[78] It is a similar logic as in fast-track DiGA or PEC-AN, however, an appropriate reimbursement model is still absent here.

SPAIN

In accordance with the ongoing trends of the healthcare sector which focus heavily on patient-centricity and value-based solutions, the digitalization of the industry has been recognised as a main priority in Spain. As the evaluation process is strictly decentralised, good selection of the region in Spain is crucial for future success.

However, the national healthcare system follows a decentralised model, where each Autonomous Community oversees their own health services, which implies that the level of digitalization widely varies between each Autonomous Community. Therefore, regulation and financing of any digital device and/or system on a national level is challenging.[79]

To address the growing trends, the Spanish National Health System (SNS) has prioritized the introduction of digital solutions according to their Digital Health Strategy: "Digital Spain 2025".[80] This strategy aims to develop Digital Public Services in the healthcare sector, improve the access of data through the interoperability of all information systems and boost data analysis and exploitation.

After the CE authorizations are acquired, the medical device passes through an evaluation process. As hinted above, the evaluation process is decentralised and is thus dependent on each Autonomous Community. While some possess evaluation agencies of their own, each Autonomous Community evaluates DTx on an individual basis following the same evaluation process as medical devices.[81]

Currently there are no existing reimbursement or financing regulations set in place by the public health system for DTx in Spain. Since DTx hold CE certification and are considered "medical devices", they fall under the Law of guarantees and rational use of medicines and medical devices.[82] To be reimbursed within the public health system, a device must be included in the services provided by the SNS; reimbursement has not yet however been awarded to a DTx medical product here.

[77] NICE: Early Value Assessment (EVA) for medtech; URL: https://www.nice.org.uk/about/what-we-do/eva-for-medtech; retrieved on: 15.6.2023.
[78] NICE: Eight digitally enabled therapies to treat depression and anxiety in adults conditionally recommended by NICE; URL: https://www.nice.org.uk/news/article/eight-digitally-enabled-therapies-to-treat-depression-and-anxiety-in-adults-conditionally-recommended-by-nice; retrieved on: 15.6.2023.
[79] fenin (2020): Índice Fenin de Madurez Digital en Saludů URL: https://www.fenin.es/documents/document/778; retrieved on: 17.5.2023.
[80] General Secretariat for Digital Health, Information and Innovation for the SNS (2023): Digital Health Strategy – National Health System; URL: https://www.sanidad.gob.es/ciudadanos/pdf/Digital_Health_Strategy.pdf; retrieved on: 17.5.2023.
[81] EIT Health Spain (2022): Una nueva ERA en Europa para las apps de salud: armonizando los procesos de Evaluación, Reembolso y Adopción; URL: https://vimeo.com/673139365; retrieved on: 18.5.2023.
[82] Agencia Estatal Boletín Oficial del Estado (2015): Real Decreto Legislativo 1/2015, de 24 de julio, por el que se aprueba el texto refundido de la Ley de garantías y uso racional de los medicamentos y productos sanitarios; URL: https://www.boe.es/buscar/act.php?id=BOE-A-2015-8343; retrieved on: 18.5.2023.

Despite the existing barriers, the RedETS (Red Española de Agencias de Evaluación de Tecnologías Sanitarias y Prestaciones del Sistema Nacional de Salud) is the main resource used in the evaluation of healthcare technology within the current Spanish regulatory system. The RedETS is tasked with defining the intended use of any medical technology in accordance with the European and national regulations, which then allow the classification of the risk of each DTx, as well as its value and role within the assistance process in comparison to existing devices. The use of such public entities on a national level may boost more centralised and nationwide regulatory models for DTx.

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In Chapter 7.4 of the recently released Digital Austria Act (DAA)[83], the government parties are proposing the introduction of quality approved DiGA.

[83] Digital Austria Act; URL: https://www.bmf.gv.at/dam/bmfgvat/presse/unterlagen-pressekonferenz/Digtal-Austria-Act.pdf; retrieved on 6. 10. 2023.

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