DRUG/DIGITAL COMBINATION: 6 REASONS TO MAKE THE LEAP!

Introduction

At Aptar Digital Health, we strongly believe that combining a prescription drug (Rx) with digital therapeutics (DTx) — or what we call "Digitally Augmented Therapies" — can improve the treatment value, leading to better treatment adherence for patients living with chronic conditions or receiving specific medicine.

According to EvaluatePharma[1], total prescription drug sales are expected to grow from $904Bn in 2020 to $1.4T by 2026. During the same period, $252Bn is considered at risk due to patent expiry. Rx/DTx combinations support a drug asset throughout its lifecycle, from day one on the market to the start of its decline due to the entry of generics and more competitive alternatives.

Rx/DTx combinations can even contribute before market approval, starting from phase II of clinical development. DTx can build patient-reported evidence that is needed to defend claims when the drug hits the market. For pharma, this is also an opportunity to improve the safety profile of its overall value proposition to patients and providers and increase engagement during virtual trials.

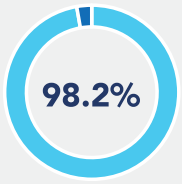
In the coming years, only accelerated by the COVID-19 crisis, we can expect DTx to form an important part of clinical and commercial development plans of future drugs. DTx builds on the drug asset and increases its intrinsic value for all stakeholders of the healthcare system. It also contributes to a longer lifespan for the asset and temporarily shields it from the decline phase.

To emphasize this point, we identified six value drivers for an Rx/DTx approach to drug development and release in the pharmaceutical industry.

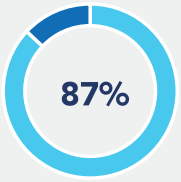
1. Address treatment complexity and toxicity

Improved management of treatment-emerging symptoms can help maximize adherence and treatment exposure. Rx/DTx combinations can provide optimal support to help identify symptoms and intervene as early as possible to mitigate dose-limiting toxicities.

In 2015, Aptar Digital Health (formerly known as Voluntis) and AstraZeneca initiated a feasibility study to test eCO, a digital companion app for women with ovarian cancer undergoing treatment in clinical trials with cediranib/olaparib combination therapy (NCI 9825)[2]. The solution was designed to support both self-management and remote management of hypertension and diarrhea. These two side effects were affecting the patient experience and causing treatment interruptions and discontinuations (between 27% and 39% for cediranib in the ICON6 trial in 2016)[3]. The study[4] demonstrated the following:



eCO captured 98.2% of required blood pressure measures



87% of diarrhea events were limited to grade 1, and no grade 3 or 4 events were reported.

Patients reported a high level of usability of the device, high satisfaction with the device, and a feeling of a close monitoring by the care team – all while being more involved in their self-care.

This study illustrates how companion apps can be used to monitor drug-related toxicities, manage these events using validated algorithms, and improve the patient experience.

Another example of the potential impact of DTx on real-world use of medication can be found in diabetes. For people living with type 2 diabetes (T2D), achieving glycemic targets as soon as possible is a key factor for better outcomes. Unfortunately, real-world data published in 2010 and 2013 in France and the US, respectively, showed that a minority of T2D patients achieve glycemic targets within 12 months. In 2019, the randomized controlled trial TeleDiab-2 explored the potential benefit of Diabeo-BI to optimize basal insulin initiation in subjects with inadequately controlled T2D. At the four-month follow-up visit, patients reported the following:

- A1c reduction was significantly higher in a group supported by the DTx and telemonitoring, compared to a standard of care group.
- Fasting Blood Glucose objective of 100 mg/dL was reached by twice as many patients in the interventional group as in the control group.
- Telemonitoring experience was positive, as 98.1% of patients equipped with the DTx solution asked to continue with the solution for up to 13 months.

Digital therapeutics such as eCO and Diabeo-BI provide support in addressing treatment complexity, dosing, and toxicity. They illustrate new strategies and solutions to help improve the patient experience and maximize exposure to treatment in view of achieving better clinical outcomes.

2. Increase differentiation

Digitally augmented therapies are new tools that can help maximize the probability for innovative drugs to succeed in the sales process and differentiate from competition. If we consider two drugs with similar efficacy and toxicity profile for the same patient population, value-added services can contribute to differentiation by delivering an optimal treatment experience to patients and care teams. The industry has been developing these strategies for more than a decade in the form of Patient Support Programs. A good example is AbbVie's Complete program5 that provides additional support to patients treated with medication targeting autoimmune diseases, such as rheumatoid arthritis or psoriasis. Programs like

this increasingly rely on digital technologies to deliver value-added services to patients. With the advent of DTx, pharmaceutical companies now have access to new channels and new technologies to deliver "beyond-the-pill" services. Moreover, investing in these winning combinations comes at a relatively low expense compared to R&D expenditure for a single drug asset. This is one reason why most global pharma companies have already shown interest in DTx companies through VC funding, partnership, co-development, or acquisitions. As of October 2021, more than 80 deals were identified, past and present, between pharmaceutical companies and DTx companies.

eCO app

Diabeo

3. Support new formulation / At-home treatment

Increasing the convenience and accessibility of innovative therapies is paramount to supporting treatment adherence and market traction. That is why more drugs traditionally administered intravenously are benefiting from subcutaneous formulations. According to a 2018 publication by Bittner and al.[6], subcutaneous formulations also show "significant advantages over intravenous administration on various parameters such as hospital and clinical cost savings, reduced time and resource use, increased flexibility in appointment scheduling, and reduced capacity bottlenecks and nursing overtime." While specific innovations like Halozyme's ENHANZE® drug delivery platform clearly represent the trend of patient empowerment and facilitation of drug administration, they raise questions about the safety and efficacy of a treatment that is now administered by patients or caregivers away from the supervision of specialized teams. The combination of a drug, a DTx, and a connected drug delivery device can help biopharmaceutical companies deliver an ecosystem of products and services with the potential to facilitate self-administration under the remote supervision of healthcare professionals.

Aptar digital health

Many pharmaceutical leaders have already strengthened their commitments to developing digitally enabled ecosystems for at-home treatments. A 2021 Molex survey[7] of 215 executives from pharma and biopharma industries found that one-third were already in the market with digital drug delivery for at least one therapy. According to the same report, there are three main drivers for pharma's interest in these approaches:

- Improved patient engagement
- Development of a competitive advantage
- Demonstration of better patient outcomes

This is the inscribed model for BetaConnect[8], a digitally enhanced version of Betaseron (Bayer, interferon beta-1b) used to treat relapsing forms of MS. Betaseron combines the drug with a connected drug delivery system and an app-based platform. The connected pen delivers a better patient experience by including guidance on how to self-inject, automatic needle insertion and retraction, and customizable injection speed and depth. The app collects injection details, patient status, and symptoms and connects the patient with a "BETA Nurse" — a member of the care team who can provide additional support to the patient whenever needed. The care team accesses patients' data through a dedicated navigator, bringing additional visibility into the course of a treatment that is self-administered by patients at home.

4. Generate incremental revenue through DTx reimbursement frameworks

A burning question regarding DTx relates to the payment model and potential reimbursement frameworks. Standalone reimbursement is not always necessary for a DTx initiative to be profitable, but new reimbursement pathways represent additional opportunities to monetize these solutions. Several payers currently cover DTx and digitally augmented therapies, paving the way for structured and scaled-up processes. Such engagement will allow broader access to these innovations.

New frameworks have emerged over the past few years, such as the ETAPES program[9] in France, the DiGA process in Germany, and the introduction of new CPT codes[10] in the US. In France, Moovcare (lung cancer) and Diabeo (diabetes) have received positive feedback from health technology assessment bodies for reimbursement; Germany's program covers 33 digital solutions[11].

Sanofi followed this strategy with Insulia® in France. As part of the "ETAPES" program, Insulia is reimbursed based on a set of eligibility criteria up to 940€ per patient per year (pppy), split between the solution provider (600€ pppy) and healthcare professionals (340€ pppy). These initiatives demonstrate that DTx can be a source of direct revenue for life science companies alongside drugs and traditional medical devices.

5. Support value-based contracting

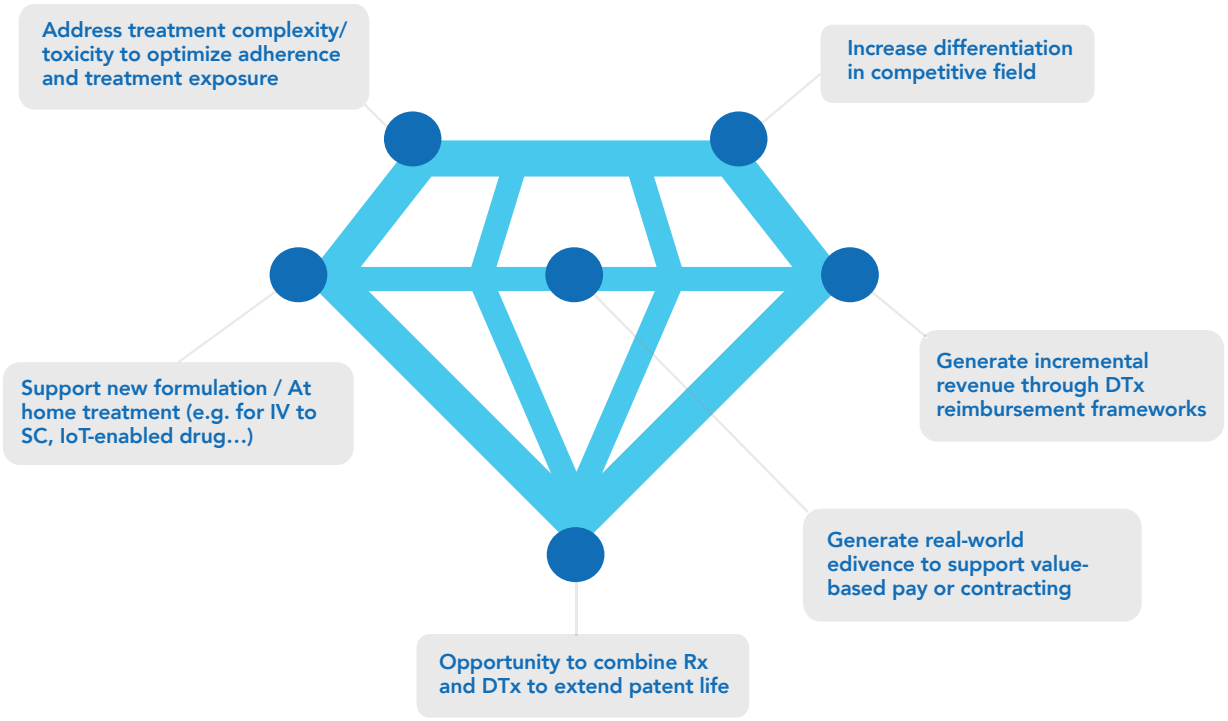
Healthcare expenditures have been rising across the globe, representing up to 20% of some countries GDP. In 2020, the U.S. spent $4.1 trillion on healthcare, which amounts to $12,530 per capita[12]. Cost increase poses real threats to medical care accessibility. Therefore, many policymakers and health economists have been advocating for value-based care (VBC) models where healthcare products and services are paid based on the actual value they deliver in the real world. In this model, manufacturers and providers are incentivized to focus on the quality of products and care they deliver to patients. This paradigm shift impacts the entire healthcare value chain — including pharmaceutical companies, who could be paid less if their therapies are proven to be less effective in the real world than expected based on clinical trials.

Conversely, value-based care is an opportunity for pharmaceutical players to deliver complementary value-added services promoting better patient outcomes. And digital technologies and DTx can help. They present two major benefits as both a measuring tool and a mitigation:

- The DTx can collect patient health information to measure drug efficacy, toxicity, and the patient's adherence.
- The insights and/or interventions the DTx delivers can lead to better clinical decisions, optimizing outcomes in real-world settings.

Recently, Prime Therapeutics agreed to an outcomes-based arrangement for the treatment with Advate of Hemophilia A. In such an arrangement, real-world clinical outcomes and cost implications are assessed, and the health plan remuneration model is based on the level of certain quantifiable medical costs associated with unsuccessful treatment under a total cost of care model[13]. In parallel to this initiative, Takeda has implemented the myPKFiT Mobile App[14], a patient-centric solution that aids in personalizing a patient's prophylaxis dose and schedule in the real world, contributing to ensuring successful outcomes for patients, payers, and the manufacturer.

In a value-based world where payments for drugs are tied to real-world clinical outcomes, it becomes critical for pharmaceutical companies to measure, personalize, and improve the actual treatment experience. DTx specifically designed to address these needs can play an important role in securing access and reimbursement for the corresponding drug asset.



6. Combine Rx and DTx to extend patent life

Patents for drugs typically confer 20 years of protection after invention, but half of that timeframe is absorbed by R&D. When a drug is eventually commercialized, it has around 10 years to make a dent and become profitable. After this period, generics come in and can drop brand sales by as much as 80%. Therefore, any opportunity to protect intellectual property through exclusivity and patents is critical to the industry.

In the past, new formulations, modes of administration, expansions of indication to new populations, and drug-drug combinations were traditional strategies to delay the "patent cliff." Additional strategies based on the combination of drugs with innovative medical devices to complement and enhance treatment can also achieve this objective. As DTx are regulated as medical devices, they could represent an opportunity to extend protection through new patents. For branded drugs generating revenues in billions of dollars per year, one year of additional protection would have a substantial impact on the drug valuation. Even if it is not a DTx per se, the story of the Japanese drugs manufacturer Otsuka and the sensor company Proteus that led to the development of the connected pill Abilify MyCite® is compelling[15]. When these companies started to work together, value was expected from an innovative IP strategy.

The "digitally enhanced" version of the drug would be protected for much longer than its old, non-connected counterpart that has already fallen from the patent cliff. Insulin manufacturers pursue similar approaches by developing connected ecosystems in anticipation of the entry of biosimilars.

Some have already argued that the connected system, not the drug, should be considered when assessing interchangeability. Regulators should not consider only the insulin itself, but its combination within a digital ecosystem to determine whether a biosimilar may be substituted for the reference product safely and effectively without the involvement of the prescriber. While life cycle management and patent strategies based on Rx/DTx are not yet mature, pharmaceutical leaders should consider this potential value driver carefully.

DTx as a value driver for pharma drug assets

Digitally augmented therapies such as DTx address a variety of clinical and business challenges:

- Mitigate treatment complexity or toxicity to optimize treatment exposure.
- Deliver differentiating treatment experiences to patient and care teams.
- Support the safe and effective transition from hospital-based treatment to at-home treatment.
- Generate incremental revenue through innovative reimbursement frameworks for digital therapeutics.
- Measure and improve real-world outcomes to support outcomes-based contracting.
- Extend exclusivity through proprietary Rx/DTx combinations.

DTx delivers value for pharma all along the lifecycle of their drug assets, from advanced clinical development phases up to maturity and end of life.

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insulia

Insulia® is a prescription-only software medical device intended for use by healthcare professionals and their type 2 adult diabetes patients as an aid in the management of diabetes. Insulia is only indicated for use with insulin detemir (Levemir U-100) once or twice daily, insulin degludec (Tresiba U-100) once daily, insulin glargine (Basaglar U-100, Lantus U-100, Semgle U-100 and Toujeo U-300) once daily, and Human NPH once daily. Insulia should not be used for premixed insulin. Insulia should not be used in the following populations: pregnant women; non-adult patients; patients that are treated with a basal plus or a basal, bolus regimen (i.e multiple mealtime insulin injections per day or insulin pump therapy). Please carefully read product instructions, and if in doubt, please consult your care team before use. To learn more, please visit: www.insulia.com

Aptar Digital Health provides enhanced treatment experiences that empower patients to be more active in their treatment journey. Leveraging our diverse portfolio of regulated products and services and strategic partnerships with global digital health organizations, our holistic ecosystem of physical and digital interventions are customized to every unique treatment journey. These solutions offer differentiating experiences to patients and providers across therapeutic areas to help them achieve higher quality care and more positive outcomes.

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