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HEALTH CARE DELIVERY SYSTEMS AND IMPLEMENTATION IN DIABETES (ME MCDONNELL AND AR SADHU, SECTION EDITORS)

USA Vs Europe: Who Is Leading the Diabetes Tech Race?

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Abstract

Purpose of Review To highlight global advancements in diabetes technology and compare available technologies and device approval processes in the USA and Europe and their impact on safety and innovation.

Recent Findings The last two decades have seen a rapid growth in diabetes technology driven by the impetus to improve glycemic control, avoid complications of insulin therapy, improve quality of life, and hand more autonomy to individuals with diabetes. Meanwhile, changes to regulatory processes in the USA and Europe aim to facilitate entry of new devices into the marketplace.

Summary Major strides have been made in digitization of insulin pens, continuous glucose monitors and their integration with insulin pumps, automated insulin delivery systems, and closed-loop insulin pump systems. The centralized regulatory body in the USA and more decentralized approval bodies in Europe have led to differences in the rate of market availability of diabetes devices. While both US and Europe systems have different advantages and disadvantages in device approval, they continue to struggle with balancing accelerated device access with adequate clinical evidence and monitoring to ensure safety of such devices.

Keywords Diabetes technology · Europe · United States · Insulin pump · Continuous glucose monitor · Approval process

Introduction

While looking through the history of diabetes management from early to modern day, it becomes apparent that technology in diabetes management has advanced significantly. From the early techniques of testing glucose in urine with Benedict's solution to the modern-day hybrid closed loop insulin pump, technology has become ingrained in the daily lives of patients with diabetes and providers alike.

Historically, diabetes and its symptoms were first described dating back to 1550 BCE in Egyptian papers, with further references to this disease being present in multiple cultures including the Indians, Persians, and Chinese. The first breakthrough was the discovery of insulin by Banting, Best, and McLeod in 1921 that provided the first available treatment [1, 2]. Throughout the years, additional milestones in therapy occurred with the development of oral medications in the 1950s. It was not until 1965 when Anton Hubert Clemens invented the first blood glucose meter that determined the levels by reflecting light from a test strip [3]. Also, in this decade, Dr. Arnold Kadish invented the first prototype of an insulin pump; it was the size of a backpack and delivered insulin and glucagon to the patient. In 1973, Dean Kamen took the concept of the insulin pump further when he invented the first wearable infusion pump. Since then, diabetes technology continued to improve with many advancements along the way. In 1999, the FDA approved the first continuous glucose meter that collected data for 72 h. This was later followed by the GlucoWatch, the first real-time glucose monitor that was improved upon by Medtronic and Dexcom with their

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versions of real-time continuous glucose monitoring (CGM) systems [3]. Since that time, both insulin pumps and CGMs have made remarkable transformations to today's current models.

The aim of novel diabetes technology is to enhance patient care by providing better blood glucose and hemoglobin A1c (HbA1c) control, decreasing hypoglycemia rates, and overall improving their quality of life. Today, in addition to the traditional companies focused in diabetes care, entrepreneurs with solid financial background are bringing new options to the market. The race for more advanced technology is a worldwide phenomenon currently led by the USA and Europe. In this paper, we will discuss the differences in access to diabetes technology between the USA and Europe, focusing on the available technology and the approval process for these devices in both markets at the time of writing this manuscript.

Diabetes Technology Currently Available in the USA and Europe

Devices for diabetes care can be divided into 3 major categories, each with its own utility, indications, contraindications, and accessibility: digital insulin pens, CGM systems, and insulin pumps.

Digital Insulin Pens (Table 1)

Digital insulin pens were designed for insulin-dependent individuals undergoing multiple daily subcutaneous injections [4, 5]. The most important features of the currently available "smart" pens include dose tracking (memory function) and Bluetooth connectivity, allowing real-time data transfer to a smartphone app [4–6]. Compared with the Pendiq 2.0 in Europe, which is meant to keep a digital, accurate, and easily accessible injection diary, the Inpen system available in US markets includes a dose calculator which provides recommendations based on previous insulin doses, active insulin-on-board, current blood glucose levels, and carbohydrate intake. Furthermore, the Inpen app can be connected to Dexcom G5 and G6 CGMs [4]. On the other hand, the widely available Clipsulin C3 is an insulin dose-recording device that clips to the dosage knob in most disposable and refillable pens. It retrieves injection information and transmits it via Bluetooth to the Diabnext app that tracks insulin doses on a digital logbook, allowing for data analysis and sharing with healthcare providers [6]. With respect to dose guidance and tracking, digital insulin pens are more affordable and easier to use compared with insulin pumps.

Table 1 Overview of currently available digital ("smart") insulin pens

Device	Age	Labeling	Medicare coverage in the USA	Length of use	Type of insulin for use with device	Digital platform: consumer vs HCP		Available for use in	
						Consumer	Healthcare provider	USA	Europe
InPen by Companion Medical	12+	For patients undergoing multiple daily subcutaneous injections	Yes	1 year	Lilly Humalog and Novo Nordisk Novolog	InPen App	No	Yes	No
Pendiq 2.0 by Diamesco	14+	Keeps injection diary digitally and automatically	No	3 years	3 mL cartridges from Sanofi-Aventis, Lilly, Novo Nordisk, Berlin-Chemie	Dialife App	No	No	Yes
Clipsulin C3 by Diabnext	N/a	Keeps injection diary digitally; does not require prescription	No	Indefinite	Connects to most disposable and refillable pens in the market	Diabnext App	Diabnext Pro	Yes	Yes

Specifications and differences between devices are displayed

HCP, healthcare provider

Continuous Glucose Monitoring Systems

CGM is a method to track glucose levels over time. CGM systems take glucose measurements at regular intervals, 24 h a day, and translate the readings into dynamic data, generating glucose direction and rate of change. This information helps to better guide insulin therapy, leading to a significant reduction in A1c levels and hypoglycemia events, whether users are on insulin injections or on pump therapy [7, 8, 9••].

Most CGM systems are available both in the USA and in Europe. The Medtronic Guardian Sensor 3 allows for sensor-integrated pump therapy with the MiniMed 670G, 630G, and 640G systems and also powers Medtronic's Guardian Connect CGM system, which provides predictive high/low alerts 10–60 min prior to their occurrence [10, 11]. The Dexcom G6 is factory-calibrated and approved to use without confirmatory fingersticks for calibration, as is Abbott's FreeStyle Libre [12, 13]. The latter includes a handheld reader and a disposable sensor that can be scanned as often as the user wants; however, it does not have automated alarms [13]. This is not an issue with Libre's newer version, the FreeStyle Libre 2, which offers optional and individually adjustable high/low alarms [14]. It is only available for sale in Germany at the time of writing of this manuscript.

Senseonics' Eversense (USA only) and Eversense XL (Europe only) are longer-term CGM systems that use fluorescence technology to measure glucose with a subcutaneously implanted sensor that can be worn up to 90 and 180 days, respectively [15, 16]. High/low glucose alerts are customizable and can be visual, auditory, and vibratory via the transmitter. Lastly, Medtrum's CGMs are offered in Europe and the A6 TouchCare system enables pump integration [17]. Table 2 shows an overview of the currently available CGM systems, including specifications and differences between devices.

Insulin Pumps

Continuous subcutaneous insulin infusion therapy has rapidly evolved over the past decade and far more options are now available for patients with type 1 and type 2 diabetes who seek better control of their disease. Insulin pumps have been shown to reduce HbA1c levels without an increased risk of hypoglycemia compared with a regimen of multiple daily insulin injections [18]. Moreover, sensor-augmented pump therapy results in better glycemic control in both adults and children with uncontrolled type 1 diabetes [19]. This information has led the major companies and several entrepreneurial projects around the world to explore and develop novel technologies for diabetes treatment.

Medtronic's MiniMed 670G is the first and only commercially available hybrid closed-loop system to the date of this writing. Its SmartGuard technology features two levels of automated insulin delivery: Auto Mode, which automatically adjusts basal insulin every 5 min based on CGM readings, and Suspend Before Low, which stops insulin before reaching preset low limits and automatically restarts it when glucose levels recover [20]. The MiniMed 630G, available in the USA, and its European counterpart, the MiniMed 640G, also offer CGM integration and SmartGuard technology with Suspend Before Low feature and high/low predictive alerts [21, 22]. The Bolus Wizard calculator recommends precise bolus doses based on current glucose reading, active insulin, and user-entered carbohydrate intake.

Only two other insulin pumps support CGM integration: Tandem's t:slim X2 and Medtrum's A6 TouchCare system. The t:slim X2 pump integrates with the Dexcom G6 system; its Basal-IQ technology predicts glucose levels 30 min ahead, suspending insulin delivery if expected to drop below 80 mg/dL and resuming it once glucose rises [23]. Likewise, the A6 TouchCare system includes a patch pump and CGM, providing a semi-closed loop with Predictive Low Glucose Suspend [17].

Insulet's Omnipod system and the newer Omnipod DASH (USA only) have two components: the Pod, a small, tubeless, and refillable device which provides up to 3 days of insulin delivery and a handheld personal diabetes manager (PDM), which wirelessly manages the insulin delivery through the Pod [24, 25].

Compared with the American market, there are quite a few additional options in Europe when it comes to insulin pumps (Table 3) [26–30]. Just recently, in March 2019, the Cellnovo system was discontinued by the manufacturers. One device exclusively available in the USA at this time is the V-Go, indicated for adults with type 2 diabetes requiring insulin therapy [31]. V-Go is a patch-like pump with three available options (20, 30, 40), each referring to the amount of insulin delivered at a continuous preset basal rate during a 24-h period. Additionally, mealtime boluses are delivered by clicking a button; each click delivers 2 units of insulin with a max of 36 units a day.

Upcoming Cloud-Based Platforms for Closed-Loop Systems (Table 4)

In recent years, it has become known within the type 1 diabetes community that a certain "security flaw" in discontinued insulin pumps could enable the use of homemade algorithms with the purpose of achieving a hybrid closed-loop system; this phenomenon is called "looping." Today, many different sites such as Nightscout, OpenAPS, DIY Loop, and AndroidAPS focus on this topic. Still, none of these algorithms are currently FDA-approved [32].

In Europe, Diabeloop was approved by the European Medicines Agency (EMA) and its launch is expected soon. This system will use the Kaleido pump and the Dexcom G6

Table 2 Overview of currently available CGM systems

Continuous glucose meters

Device	Age	MARD (%)	Fingerstick calibration	Warm up for device	Medicare coverage in the USA	Length of use	Features	Digital platform: consumer vs HCP		Available for use in	
								Consumer	Healthcare provider	USA	Europe
Medtronic Guardian Sensor 3	14+	8.7	2/day minimum	2 h	No	7 days	Powers Medtronic's SmartGuard technology, predictive alerts	No	CareLink software	Yes	Yes
Medtronic Guardian Connect	14+	8.7	2/day minimum	2 h	No	7 days	Real-time glucose tracking, predictive alerts	Guardian Connect App	CareLink software	Yes	Yes
Dexcom G6	2+	9.0	0 (factory calibrated)	2 h	Yes	10 days	High-low alarms, provides glucose trend, simple auto-applicator	Dexcom G6 App	Dexcom CLARITY system	Yes	Yes
Abbott's FreeStyle Libre	18+	9.4	0 (factory calibrated)	1 h	Yes	14 days	Handheld reader, provides glucose trend, shareable reports	FreeStyle LibreLink App	LibreView system	Yes	Yes
Abbott's FreeStyle Libre 2	4+	9.5	0 (factory calibrated)	1 h	No	14 days	Handheld reader, provides glucose trend, high-low alarms	FreeStyle LibreLink App	LibreView system	No	Yes
Senseonics Eversense	18+	8.5	2/day minimum	24 h	No	90 days	Long-term use; visual, auditory and vibratory alerts; shareable results	Eversense Mobile App	Eversense DMS	Yes	No
Senseonics Eversense XL	18+	8.5	2/day minimum	24 h	No	180 days	Long-term use; visual, auditory and vibratory alerts; shareable results	Eversense XL App	Eversense DMS	No	Yes
Medtrum A6 TouchCare and S7 EasySense	2+	9	2/day minimum	2 h	No	7 and 14 days	Semi-closed loop system with A6 pump, predictive low glucose suspend	EasyTouch, EasySense	EasyView	No	Yes

MARD, mean absolute relative difference

Table 3 Overview of currently available insulin pumps

Device	Age	Battery	Reservoir	Infusion set change frequency	Basal/bolus ranges	CGM integration	Features	Available for use in:	
								USA	Europe
Medtronic 670G	7+	AA battery × 1	3.0 mL (300 U)	2–3 days	Ba, 0.025–35 U/h Bo, 0.025–25 U	Yes	SmartGuard technology, hybrid closed loop system, Auto mode	Yes	Yes
Medtronic 630G	14+	AA battery × 1	3.0 mL (300 U)	2–3 days	Ba, 0.025–35 U/h Bo, 0.025–25 U	Yes	SmartGuard technology, Bolus Wizard calculator, predictive alerts	Yes	No
Medtronic 640G	7+	AA battery × 1	1.8/3.0 mL (180/300 U)	2–3 days	Ba, 0.025–35 U/h Bo, 0.025–75 U	Yes	SmartGuard technology, Bolus Wizard calculator, predictive alerts	No	Yes
Tandem t:slim X2	6+	Lithium polymer battery	3.0 mL (300 U)	2–3 days	Ba, 0.1–15 U/h Bo, 1–25 U	Yes	Basal-IQ technology, rechargeable battery, waterproof	Yes	Yes
Insulet Corp. Omnipod (DASH)	All ages	Pod: battery integrated PDM: AAA × 2	200 U	Built-in cannula up to 72 h	Ba, 0.05–30 U/h Bo, 0.05–30 U	No	No tubing, handheld Personal Diabetes Manager (PDM)	Yes	Yes (Omnipod only)
SOOIL Dana Diabecare RS/R/IIS	7+	3.6v DC lithium battery × 1	3.0 mL (300 U)	2–3 days	Ba, 0.04–16 U/h Bo, 0.1–80 U	No	Smallest pump, remote control with built-in BGM (R)	No	Yes
Medtrum A6 TouchCare pump	2+	Pump: button cell battery × 2 PDM: AAA × 1	2.0 mL (200 U)	Patch pump, replace every 2–3 days	Ba, 0.05–10 U/h Bo, 0.05–25 U	Yes	No tubing, semi-closed-loop system, predictive low-glucose suspend	No	Yes
Roche Accu-Chek Combo pump	All ages	AA battery × 1	3.15 mL (315 U)	2–3 days	Ba, 0.05–50 U/h Bo, 0.1–50 U	No	Handset with built-in BGM and bolus advisor, option for data transfer to computer	No	Yes
Roche Accu-Chek Insight pump	All ages	AAA battery × 1	1.6 mL (160 U)	2–3 days	Ba, 0.02–25 U/h Bo, 0.05–50 U	No	Handset with built-in BGM and bolus advisor, pre-filled insulin cartridges	No	Yes
YpsoMed mylife YpsoPump	All ages	AAA battery × 1	1.6 mL (160 U)	3 days	Ba, 0.00–40 U/h Bo, 0.1–30 U	No	Small insulin pump with touchscreen, pre-filled insulin cartridges	No	Yes
ViCentra Kaleido pump	All ages	Integrated rechargeable battery	2.0 mL (200 U)	3 days	Ba: 0.05–5 U/h Bo: 0.05–20 U	No	Set of two rechargeable pumps and a handset, micro-pulse insulin delivery	No	Netherlands only
Valeritas V-Go device	Adults with T2DM	No battery	Total insulin, 56, 66, 76 U	Replace pump every 24 h	Ba: 20/30/40 units Bo: 2 U (up to 18x)	No	No tubing, insulin delivery with button presses, waterproof	Yes	No

U, units; *Ba*, basal; *Bo*, bolus; *BGM*, blood glucose meter; *T2DM*, type 2 diabetes mellitus

Table 4 Upcoming platforms for hybrid closed-loop systems

Company	Compatible pump/Sensor	Brief description	Available for use in	
			USA	Europe
Diabeloop	Kaleido pump/ Dexcom G6	Diabeloop Generation 1 (DBLG1) is the second hybrid closed-loop system to be approved by EMA. This system uses a locked down smartphone with an algorithm that receives data from the CGM and sends commands to the insulin pump for adjustments.	No	Yes
Tidepool	In development; has partnerships with Medtronic, Omnipod and Dexcom	Tidepool Loop is an upcoming web-based algorithm that will be formatted as a smartphone app that connects with CGMs and insulin pumps from different brands.	No[a]	No

[a] In submission for FDA approval

EMA, European Medicines Agency

sensor with plans to expand to other devices in the near future [33, 34]. Another upcoming hybrid closed-loop system is Tidepool's Loop [35]. Tidepool is a non-profit organization best known for their free online software for diabetes management; their Loop will integrate CGMs and insulin pumps from different brands using a web-based algorithm. The company's goal is to get this system FDA-approved in the next 1–2 years.

Device Approval in the USA and European Union

Device Approval Process in the USA

The Food and Drug Administration (FDA) was given authority to regulate medical devices in the USA starting in 1976. The FDA stands out from many of its global counterparts in its near absolute power to regulate; many organizations, such as the EMA, have a far more decentralized process to approve medical devices. This section briefly summarizes the general processes for medical device regulation by the FDA and EMA to equip practitioners with insight regarding what approval abroad does—and does not—mean for patients.

While the FDA requires all devices to follow general control requirements (such as registration and device listing), further regulations depend on the device classification [36]. The FDA classifies all medical devices into three main categories according to risk; class I is low risk, class II is intermediate risk, and class III is the highest risk classification. The majority of class I devices are exempt from pre-market submission and do not require clinical evidence before marketing [37]. Class II and class III are subject to more rigorous regulations. For instance, class II and class III devices are subject to general and special controls such as device-specific labeling and mandatory performance standards.

One feature of the US system is the utilization of the so-called predicate devices to influence approval of class II and class III devices. Manufactures can bring such devices to market following one of several pathways. The most common is called premarket notification (PMN) or 510(k) review, which is a shorter and less expensive pathway in which the FDA determines if a "device is substantially equivalent to a device already on the market (predicate device)" [36]. A second pathway requires premarket approval (PMA) and is the most stringent review process. During this type of review, the FDA determines "if the device is reasonably safe and effective for its intended use," which requires stronger clinical evidence [36]. Additional approval pathways include de novo approval which applies to devices which lack a predicate meeting the class II or class III designations and Humanitarian Device Exemption (HDE) which applies to class III devices needed to benefit patients with rare disease conditions [38]. Most insulin pumps are classified as class II devices by the FDA, although those integrated with CGM systems are classified as class III devices [39]. Once devices are approved, they are subject to post-market regulations and surveillance [40]. These include requirements for hospitals, device users, and health professionals to report adverse device-related events to the manufacturer and directly to the FDA [39].

It is important to clarify the level of clinical evidence required for device approval (class II and class III devices). Up to 75% of class II devices require clinical evidence to show safety [41]. More than half of class II (and some class I) devices require 510(k) review. While class III devices are subjective to the rigorous PMA pathway, in actuality, a majority of class III devices have been cleared on the basis of 510(k) review. Level I or level II evidence is required for the majority of class III devices whereas less stringent clinical evidence is needed for the majority of class II devices or those approved through the 510(k) process [40]. Level I evidence includes high-quality randomized control trials or systematic review while level II evidence includes lesser quality RCTs, prospective comparison studies, or systematic reviews of level II studies [40]. Overall, however, the clinical evidence needed for device approval is less rigorous when compared with the level of evidence required for drug approval. This largely stems from the nature of medical devices, which renders blinding/randomization difficult or unfeasible. Additionally, the use of

predicate devices for approval opens newer devices to easier approval even if the devices may not be true equivalents and warrants individual re-evaluation [40]. Although many scholars laud the benefits of a streamlined process for device approval, one potential drawback is the problem of "serial predicates" where a new device can be approved by prior approvals of predicate devices—far removed from the original device that was approved [40].

The above regulatory pathways can certainly slow advancement of medical device development. The frustration with such delays in market availability came to head earlier this year when the FDA made a dramatic decision. For years, the Do-It-Yourself diabetes community and tech activists had been "hacking" diabetes technology to develop non-FDA-approved closed-loop systems [42], described as "looping" in earlier paragraphs. Non-profit organizations like Tidepool used this momentum and even pushed for FDA approval of apps such as Loop (designed for DIY automated insulin devices), as well as observational studies to look at the effectiveness of this technology [42]. Finally, on February 14, 2019, the FDA-approved Tandem Diabetes Care t:slim X2 insulin pump with interoperable technology through the de novo pathway [43]. This alternate controller enabled, or ACE insulin pump, is the first of its kind and allows the pump to be used in conjunction with adjunctive diabetes technologies such as CGMs, automated insulin dosing (AID) systems, blood glucose meter, and mobile applications, essentially making different medical devices interchangeable and maximizing opportunities to customize a closed-loop system. By approving Tandem's ACE pump in the new regulatory classification, the FDA effectively opened the door for developers to collaborate and bring to market such compatible systems and devices that meet the new general and special controls though the more efficient 510(k) process [43]. Ultimately, the demand for quicker approval of such systems and also safety concerns of such non-FDA devices likely pushed the FDA to change its views on such diabetes tech leading to their recent decision [43]. This decision carries the potential to usher in a new period of rapid diabetes tech advancement that is hopefully for the better.

Device Approval in the EU

At a macro-level, medical device approval in the EU differs from that in the USA in one major way: the approval process is decentralized with multiple regulatory agencies involved in device approval. The EMA was established in 1995 to harmonize regulatory bodies that were already established in EU member states [41]. Member states have two primary regulatory agencies, the state's Competent Authority and accredited notified bodies (NBs). Each state's Competent Authority assesses and ensures medical devices are compliant with the European Commission (EC) directives/regulations. Once this approval is received, manufacturers hire private NBs to mark the device as *Conformite Europeenene* (CE) for a fee. All marketed devices in the EU require a CE mark which allows them to be on the market in all EU member states. Importantly, the CE mark does *not* ensure quality of a device and only indicates compliance with European legislation [41]. The EMA works with these other regulatory bodies and provides scientific opinions/evaluation to NBs if a particular device warrants further scrutiny [44].

Similar to the US system, the EC classifies devices as low risk or class I and moderate to high risk (class IIa, IIb, and III). Moderate- and high-risk devices require scientific evidence for approval. Additionally, as in the USA, data from predicate devices can facilitate approval without additional clinical studies. Scientific evidence standards are guided by globally accepted standards like the ISO 14155:2011. Insulin pumps are classified as class IIb devices in the EU and go through the above agencies for approval [39]. Post-marketing surveillance of adverse events is recorded in a database called the European Database on Medical Devices (EUDAMED) but are not generally available to the public.

Although the decentralized EU process was once thought to lead to substantial reductions in time from development to market, the timelines for device approval do not differ as much as previously thought [41]. While devices requiring PMA lag behind EU device approval pathways by 3 years, when devices are approved through the 501(k) process (as most are), the lag time is closer to 18 days [41]. Additionally, while device approval in the EU may be quicker, market availability tends to be faster in the USA as devices approved in the EU must clear additional bureaucratic hurdles such as reimbursement approval from both insurance companies and national formularies prior to patient availability [41].

Of course, rapidity in approval may carry some drawbacks. While in the USA all medical devices should not only have evidence to support safety but also efficacy, in the EU, devices only need to show safety and performance and not clinical efficacy. That said, a lack of rigorous clinical evidence plagues both US and EU systems. Efforts are underway in both regions to address deficits in device approval processes.

Conclusion

There is evidence that diabetes technology can help improve outcomes and quality of life for people with diabetes [45]. As described above, a variety of products are available commercially and several more are in the pipeline. Globally, the USA appears to be the largest market for use of diabetes technology as trends of usage across Europe are increasing [46, 47]. Despite the differences in regulatory and approval processes between the two locations, the newer products end up hitting the markets at similar times due to the aforementioned

nuances. Recent safety concerns with hip and breast implants have helped identify critical inadequacies in the device approval processes globally. Following a global investigation by the International Consortium of Investigative Journalists (ICIJ), significant changes are being incorporated in the device approval processes and additional efforts to increase transparency for consumers have been adopted [48, 49]. An analysis of the US Manufacturer and User Facility Device Experience (MAUDE) database by the ICIJ found more than 1.7 million device-related injuries and almost 83,000 deaths [49]. It thus becomes imperative that a safe, reliable, and transparent platform is provided for both patients and caregivers using diabetes technology. Nonetheless, the process to "rectify" the safety concerns is convoluted and time-consuming layered with bureaucracy. With increased regulatory oversight and enhanced public awareness, a standardized approach toward safely acceptable technology is a matter of time. These regulatory changes might help narrow down the gap between the available technology in both continents and hence, globally. The ultimate goal of manufacturers and regulatory agencies across the globe is to provide safe, effective, and readily accessible diabetes technology for all patients.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

Human/Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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