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REVIEW

Wearable Devices for Subcutaneous Delivery of Large-Volume Biologics: Design, Use, and Regulatory Perspective

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Abstract

Biological therapies are transforming the treatment landscape for chronic, autoimmune, and oncological diseases. However, delivering large-volume, high-viscosity biologics subcutaneously remains challenging with conventional approaches. Wearable on-body drug delivery (OBDD) devices address these limitations, enabling patient-administered, home-based delivery of therapeutic volumes exceeding 5–20 mL. This review provides a comprehensive synthesis of OBDD design, product engineering principles, clinical applications, and regulatory considerations. Recent innovations, including adaptive fluidics, electromechanical actuation, and MEMS-based delivery systems, are enhancing precision and usability. Clinical case studies across oncology, immunology, rare diseases, and metabolic disorders demonstrate improved patient outcomes and adherence. Key challenges, such as fluid dynamics, tissue resistance, human factors, regulatory harmonisation, and environmental sustainability, are critically examined. Looking ahead, OBDDs will increasingly integrate digital health technologies, MEMS-based control, and eco-design strategies to support evolving therapeutic needs, including gene and RNA-based therapies. As biological formulations advance, OBDDs are poised to reshape drug delivery paradigms, offering scalable, safe, and patient-centred alternatives to traditional infusion-based care.

Keywords Wearable on-body drug delivery (OBDD) systems · Large-volume subcutaneous biologics · Drug–device combination · Patient-centric drug delivery · On-Body injectors

Introduction

Biological therapies have transformed the treatment paradigm for chronic autoimmune and oncological diseases. According to the World Health Organization, biologicals, or biologics, are medicinal products that contain one or more active substances made by or derived from a biological source [1]. Unlike traditional small-molecule drugs, which tend to act broadly, biologics are often highly targeted and engineered to modulate specific molecular pathways involved in disease processes. This selectivity has led to improved therapeutic outcomes, including better disease control, fewer adverse effects, and, in many cases, disease remission or slowed progression [2–5].

Due to their structural complexity and susceptibility to enzymatic degradation, biologics must be administered parenterally to preserve bioactivity and ensure systemic availability [6]. Common parenteral routes include intravenous (IV), intramuscular (IM), and subcutaneous (SC) delivery. However, these approaches, particularly IV administration, typically require clinical oversight and trained personnel, posing logistical barriers to frequent or long-term treatment adherence [7, 8]. Whilst IM injection is technically feasible, it is generally suboptimal for biologics due to volume limitations, inconsistent absorption profiles, and a higher risk of injection site discomfort. Consequently, IM delivery is rarely used for high-volume biological therapies. In contrast, there is a clear shift toward SC delivery, which offers improved patient convenience, supports home-based self-administration, and reduces healthcare utilisation. Amongst advanced SC delivery technologies, OBDDs offer a unique

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combination of advantages. Whilst handheld auto-injectors are limited to small-volume, rapid bolus injections and infusion pumps, though capable of continuous delivery, are typically bulky, complex, and require clinical oversight, OBDDs enable programmable, large-volume (5–20 mL or more) biological delivery in a compact, wearable format. This allows patients to self-administer therapies comfortably at home, bridging the gap between clinic-based infusion and patient-centric biological delivery.

The timeline in Fig. 1 summarises major advances in the development of subcutaneous (SC) delivery for monoclonal antibodies (mAbs). Prior to 2010, high-viscosity formulations, injection volume constraints, and a lack of regulatory pathways limited SC viability. Between 2010 and 2015, formulation advancements, such as the use of hyaluronidase (rHuPH20) co-formulation, enabled higher concentration SC products and improved absorption [9, 10]. Concurrently, initial regulatory guidance from EMA and FDA catalysed further development. From 2015 to 2020, device engineering improvements led to wearable injectors capable of delivering > 5 mL over extended periods and user-centric auto-injectors that improved adherence. Since 2020, SC delivery has reached industrial scale, with approval of multiple blockbuster biologics, optimised fill-finish technologies, and digital health integration supporting at-home administration and real-world data capture [11].

Historically, IV delivery has dominated the administration of biological agents, especially in oncology and chronic inflammatory disease management [12]. Yet, there is a clear shift toward SC delivery, motivated by its potential to enhance patient convenience, reduce healthcare utilisation, and enable home-based self-administration [13–16]. SC administration supports expanded access to therapy, but it also introduces formulation and delivery challenges [15–17]. As biological therapies evolve toward patient-centric delivery models, converting large-volume intravenous (IV) dosages to subcutaneous (SC) administration, or designing novel SC regimens that exceed the volume limitations of traditional delivery devices, necessitates the use of advanced large-volume SC platforms [18]. These constraints often necessitate high-concentration formulations, which are associated with increased viscosity, injection force, and manufacturing complexity [19, 20].

To address these limitations, advanced SC delivery technologies have emerged. These include three major device classes: handheld auto-injectors, infusion pumps, and OBDD systems. Each modality offers unique functionality, ranging from rapid bolus injection to extended infusion, and plays a specific role in optimising biological therapy delivery [18, 21, 22].

OBDDs represent a particularly promising solution for overcoming the limitations of high-dose SC administration [23]. These wearable, combination drug-device products integrate a reservoir, infusion mechanism, and user interface to deliver large volumes (5–20 ml) of biologics over an extended period, typically in a patient-administered, at-home setting. Compared to IV infusions, OBDDs provide greater dosing flexibility, improve patient comfort, and facilitate adherence through intuitive, hands-free operation [21, 24]. They can also accommodate drugs with higher viscosity and offer potential pharmacokinetic benefits by modulating absorption profiles [14].

Nevertheless, the development and deployment of OBDDs involve several technical and regulatory challenges. Device design must account for factors such as fluid mechanics, user ergonomics, biocompatibility, sterility, and

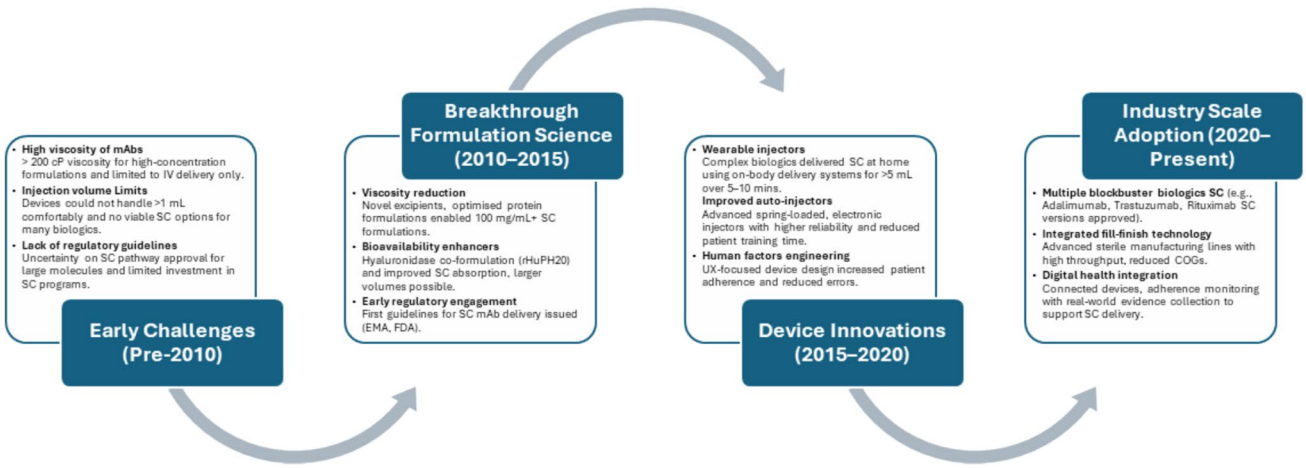

Fig. 1 Technological evolution of subcutaneous (SC) drug delivery for monoclonal antibodies (mAbs). Progression from early formulation and regulatory challenges (pre-2010), through breakthroughs in formulation science (2010–2015) and device innovations (2015–2020), to widespread industry adoption (2020–present). Key milestones include viscosity reduction, bioavailability enhancement, regulatory guidance, wearable and auto-injector advancements, and integration of digital health and manufacturing technologies

delivery accuracy [25]. Additionally, as combination products, OBDDs are subject to complex regulatory requirements that span both pharmaceutical and medical device domains, adding layers of scrutiny and coordination in global markets [26, 27]. Furthermore, given their use in uncontrolled, real-world environments, these technologies necessitate longitudinal safety and performance monitoring beyond initial market authorisation [28, 29].

Given the growing complexity of biological drugs and the trend toward decentralised, patient-centred care, OBDDs are positioned to play an increasingly integral role in the future therapeutic strategies. This review provides a comprehensive overview of SC delivery technologies with a particular emphasis on OBDDs. Following a brief discussion of auto-injectors and infusion pumps, we explore the engineering principles, clinical applications, and evolving landscape of OBDD use. We also examine real-world deployment, emerging regulatory considerations, and future innovation pathways, including digital health integration, sustainability, and policy frameworks that will shape the next generation of self-administered biological treatments.

Methods

This structured review provides a comprehensive overview of wearable OBDD devices designed for the SC administration of large-volume biological therapeutics. The review explores key aspects of OBDD development, including engineering design, clinical applications, regulatory frameworks, and emerging market dynamics. Emphasis is placed on devices intended for home-based use, with consideration of performance, usability, human factors, and integration with digital health technologies.

A systematic search was conducted in PubMed and Web of Science to identify peer-reviewed literature published by March 2025. Search strategies were tailored to each thematic area of the review and included keyword combinations such as

- "Large-volume subcutaneous delivery" AND "biologicals" AND "wearable injectors"
- "On-body drug delivery" AND "drive mechanisms" AND "electromechanical actuation"
- "Combination product" AND "regulatory framework" AND "FDA" OR "EMA"

EndNote 20.6 was used to organise references and manage citations. To ensure a comprehensive evidence base, the search was supplemented by manual review of citations in high-impact reviews, regulatory guidance documents, and white papers from biomedical device conferences.

The search was limited to English-language articles published between January 2020 and June 2025. To capture key developments in both academic and industry contexts, additional literature was sourced by manually reviewing citations within high-impact reviews, regulatory guidance documents, and white papers from biomedical device conferences.

Articles were included if they addressed one or more of the following domains: the design and operation of OBDDs for high-viscosity or high-volume biological delivery; clinical use cases spanning various therapeutic areas such as oncology, immunology, rare diseases; assessments of human factors engineering and device usability; regulatory policy and guidance related to drug-device combination products; and considerations involving market adoption, digital integration, or sustainability. Publications were excluded if they were non-English, focussed solely on small-volume injectors (less than 2 ml) not intended for large-volume biologics, or consisted of case reports that lacked engineering or regulatory insights specific to OBDDs. The retrieved literature was subsequently categorised into five thematic areas to guide synthesis and analysis: (1) engineering design and fluid dynamics, (2) therapeutic applications, (3) human factors and risk management, (4) regulatory frameworks, and (5) commercialisation and environmental sustainability.

A narrative synthesis approach was applied across the identified thematic domains to contextualise current technological advances, clinical adoption trends, and unmet challenges. Comparative tables were developed where appropriate to summarise device characteristics, therapeutic outcomes, and usability attributes.

Results

Technical Overview of On-Body Injectors

Device Classifications and Clinical Contexts

To support the rational adoption of modern parenteral drug delivery technologies, devices are typically classified into three primary categories: handheld auto-injectors, OBDD systems, and infusion pumps. The categorisation highlights divergent technological approaches and therapeutic applications, each suited to specific drug delivery demands, user capabilities, and clinical contexts. Whilst microneedle (MN) patches represent an innovative class of minimally invasive wearable devices for transdermal delivery and real-time monitoring, their application for subcutaneous delivery of large-volume biologics remains limited due to challenges in payload capacity, protein diffusivity, and formulation stability [30–32]. As such, MNs are not the focus of this review.

Table 1 consolidates the distinctions of the three categories of devices across multiple performance and user-facing

Table 1 Comparison of auto-injectors, wearable OBDDs, and infusion pumps across key technical and clinical parameters

Parameter	Auto-injectors	OBDDs	Infusion Pumps
Delivery Duration	Seconds	Minutes to 24 h [24]	Hours to weeks [21]
Volume Range	0.3–2 ml	Typically, 2–10 ml (some up to 20 mL) [21, 33, 37–39]	Up to litres [21, 35]
Flow Control	Pre-set spring- or gas-driven bolus	Pre-programmed, controlled flow [24, 34, 40]	Fully programmable, variable and continuous [21]
Drug Types	Mainly biologics, small molecules, low-viscosity solutions	Primarily biologics and high-viscosity drugs	Broad (fluids, biologics, chemotherapy, nutrients, insulin)
Route of Administration	SC or IM	SC	IV, SC, intrathecal [21, 35]
Device Size/Form	Handheld, pen-style	Compact, patch-like, tubeless	Bulky, external, often with tubing
Reusability	Single-use	Mostly single use	Often reusable (with consumables)
Patient Control	Single-button activation by user	Self-applied, minimal user interaction	Requires setup, often by professionals
Setting	Self-use anywhere (home, workplace, emergency)	Primarily home or outpatient self-use	Hospital, clinic, or home with supervision
Injection Speed	Fast (within seconds)	Slow to moderate (over minutes to hours)	Slow and sustained
Training Required	Very low	Low to moderate	Moderate to high
Typical Use Cases	Anaphylaxis, autoimmune injections, fertility, migraines	mAbs, large-volume biologics, post-chemo support	Chemotherapy, insulin, antibiotics, parenteral nutrition
Examples	EpiPen®, Enbrel® SureClick®, Humira® Pen [41–43]	Amgen Onpro®, YpsoDose®, BD Libertas™, EnFuse® [18, 24, 38]	Medtronic MiniMed®, CADD® pump, Baxter Sigma Spectrum® [21, 44]

Table adapted from Bittner et al. (2018, 2023) [33, 34], Hooven & Joughin (2017) [24], Sekiguchi et al. (2025)[21], Guo et al. (2024) [35], Enable Injections (2023) [36], and manufacturer specifications

dimensions. The development of complex biological therapies, often formulated as large-volume and/or high-viscosity products, is rapidly outpacing the capabilities of conventional subcutaneous (SC) delivery devices. Addressing this challenge necessitates innovative delivery platforms that can meet the clinical demands of modern biological treatment.

Whilst auto-injectors excel in speed and simplicity for acute or routine use, OBDDs offer scalable delivery for high-volume therapies with minimal disruption to daily life. Infusion pumps remain the gold standard for continuous, high-precision administration but require infrastructure and expertise. Together, these technologies form a continuum of delivery options supporting diverse pharmacologic, physiologic, and lifestyle requirements.

Handheld Auto-Injectors

Handheld auto-injectors are compact, pen-like devices designed for single-use administration of low to moderate drug volumes, typically ranging from 0.3 to 2 ml. These systems are spring- or gas-actuated and pre-set for rapid SC or IM injection, typically completed within seconds. This enables fast deployment in emergency or at-home scenarios with minimal training required, often limited to single-button activation [45, 46].

Auto-injectors are primarily indicated for low-viscosity biologics and small molecules and have found wide adoption in managing conditions such as anaphylaxis, autoimmune diseases, migraines, and fertility treatments [41–43, 47]. Common examples include EpiPen®, Enbrel® SureClick®, and Humira® Pens. Their key advantages are portability, ease of use, and speed. However, they are balanced by constraints in drug viscosity, volume capacity, and lack of programmable flow control.

Wearable OBDD Systems

OBDDs are skin-adhered, tubeless devices engineered to deliver moderate to large volumes, typically 2–10 ml, with some capable of up to 20 ml over extended durations ranging from minutes to hours [24]. These systems are designed for self-application with minimal user interaction and are often pre-programmed for automated or semi-automated infusion [33, 34, 44].

Compared to auto-injectors, OBDDs accommodate a broader range of biologics, including more viscous formulations such as monoclonal antibodies [34, 48]. They offer enhanced patient comfort and flexibility in non-clinical settings, enabling high-volume SC therapy without requiring clinical supervision. Representative devices include Amgen Onpro®, YpsoDose®, BD Libertas™, and Enable Injections EnFuse® devices.

Key differentiators of OBDDs include compact patch-like form factors, pre-programmed flow profiles, and

low-to-moderate training requirements [18]. These features make them ideal for chronic therapy regimens, post-chemotherapy support, and home-based biological delivery.

Infusion Pumps

Infusion pumps are programmable systems designed to deliver fluids over prolonged periods, ranging from hours to several weeks, and across various routes: IV, SC, or intrathecal. These systems accommodate a wide range of drug types and volumes, including litre-scale infusions for parenteral nutrition, chemotherapeutics, and antibiotics [49–51].

Unlike auto-injectors and OBDDs, infusion pumps are typically bulkier and require tubing, power sources, and trained personnel for setup. Whilst some models support home use under supervision, they are primarily deployed in hospitals and specialised outpatient centres. Flow control is fully programmable, allowing variable rate, continuous, or bolus administration, making them indispensable in precision dosing scenarios, such as oncology and critical care [21, 52].

Representative models include Medtronic MiniMed®, CADD® pumps, and Baxter Sigma Spectrum® devices. Their high adaptability comes at the expense of patient autonomy, portability, and ease of use.

OBDD Devices and Drive Mechanisms

OBDD devices employ one of three primary drive mechanisms: a spring-based, electromechanical, or pressure-driven mechanism. Table 2 summarises distinct drive mechanisms with their engineering approaches and clinical relevance, based on published data, manufacturer information, and real-world OBDD applications. The choice of mechanism directly impacts device performance, drug compatibility, patient experience, and cost-effectiveness.

Spring-Based Drive Mechanisms in OBDDs

Spring-based drive systems are amongst the earliest implementations in wearable injectors. They use preloaded torsion or compression springs to convert stored mechanical energy into drug propulsion through the needle [42, 61]. Their strengths lie in mechanical simplicity, reliability, and the elimination of electronic components, making them suitable for low-cost and disposable devices. However, they are limited in their ability to modulate flow rates dynamically, particularly for high-viscosity or large-volume formulations [62]. This constraint reduces their utility in home-based settings where infusion comfort, speed control, and delivery consistency are essential [63].

Table 2 Comparison of OBDDs by drug delivery mechanisms, flow rate performance, accuracy, and clinical applicability

Drive Mechanism	Representative Devices	Drug Volume Capacity	Typical Flow Rate Range	Flow Rate Accuracy	Patient Feedback/Tolerability	Clinical Applicability/Indications
Spring-Based Mechanical Drive	Neulasta Onpro® (Amgen) [53] BD Evolve™ OBI [54]	6 mL Up to 5–10 mL	~0.2–0.4 mL/min [41, 54]	Moderate; varies with tissue resistance [48, 54]	Generally well tolerated [18]; occasional site discomfort [18, 54]	Oncology (Neutropenia prophylaxis), supportive care [18]
Electromechanical Drive (Motor-Based)	West Pharma SmartDose® [24] Repatha® Pushtronex® [55]	3.5–10 mL	0.1–0.7 mL/min [24, 55]	High (±5%) [24, 51]	High patient satisfaction [55]; low pain reported [49]	Cardiovascular risk reduction (PCSK9 inhibitors), autoimmune diseases [55]
Pressure-Based System (Gas or Elastomeric Drive)	Enable Injections enFuse® [38] MicroMED dBOBi™ [56] Insulet Omnipod® [57]	10–50 mL (EnFuse® up to 20 mL) Up to 50 mL Up to 3 mL	~0.5–1.0 mL/min (adjustable by device) [56]	High (±5%) [56]; performance varies with viscosity [23, 56]	Generally well tolerated for large-volume SC delivery; positive feedback on wearability [23, 56]; minor site reactions reported [58, 59]	Rare diseases (PNH: Empaveli®), oncology, immunology, insulin delivery [59, 60]

Electromechanical Actuation Drive Mechanisms in OBDDs

Electromechanical systems use miniaturised motors to drive pistons or plungers within the drug reservoir, enabling programmable and precise control over infusion parameters [64, 65]. Activation may be manual, such as via a user-initiated button, or autonomous, and governed by embedded controllers. This approach is particularly well suited for administering viscous biologics or therapies requiring complex dosing schedules [56]. However, these systems introduce greater design complexity. The integration of motors, gears, sensors, and batteries increases both device size and manufacturing cost. Additionally, added weight and bulk can compromise wearer comfort during prolonged use, which is an important factor in patient adherence [44].

Pressure-Driven Drive Mechanisms in OBDDs

Pressure-based delivery systems utilise mechanisms such as compressed gases, elastomeric expansion, or mechanical bellows to generate force for drug expulsion [35, 66]. These devices offer passive, mechanical infusion of volumes up to 20 ml subcutaneously [59]. These systems are valued for their low energy requirements, minimal user interface demands, and mechanical simplicity [38]. However, achieving a consistent flow rate remains an engineering challenge, particularly when confronting variable tissue resistance or delivering high-viscosity formulations. Flow variability can impact both dose accuracy and patient comfort.

Each of these drive mechanisms presents trade-offs between precision, complexity, scalability, and user-friendliness. As the use of large-volume biologics expands in outpatient and home-care environments, innovation in drive system design will be central to improving delivery performance and patient quality of life. Future systems must balance performance requirements with wearability and cost, ensuring adaptability to evolving therapeutic needs and broader clinical use cases [23].

Figure 2 depicts the structural design of a wearable injector intended for (SC) self-administration of biological therapeutics. The device comprises a drug reservoir for prefilled medication, an activation button that initiates needle insertion and drug delivery, and a needle and needle cover assembly housed underneath. A safety tab prevents accidental actuation prior to placement. The device adheres to the skin via an adhesive pad, ensuring stable contact throughout administration. Drug fill markers provide visual confirmation of volume status to the user. This compact design enables SC delivery of volumes exceeding 5 mL in a controlled, user-friendly format, facilitating home-based treatment of chronic conditions with reduced burden on healthcare infrastructure.

Understanding the engineering trade-offs inherent to each drive mechanism, spanning delivery volume, dosing precision, and device portability, enables more rational alignment of platform capabilities with therapeutic needs. As drug formulations grow increasingly complex, particularly with high-viscosity biologics and personalised regimens, the selection of an appropriate drive system becomes critical to optimising both clinical efficacy and patient adherence [48, 67].

Principles of Fluid Mechanics for Large-Volume Delivery

The effective SC delivery of large-volume biologics requires meticulous regulation of key fluid dynamics parameters, namely, flow rate, injection pressure, and delivery duration [48, 62]. Unlike conventional small-volume injections, the subcutaneous delivery of large-volume and/or high-viscosity biologics must overcome the compliance and absorptive constraints of the SC tissue of the patient [68]. Optimising these parameters is critical for ensuring pharmacological

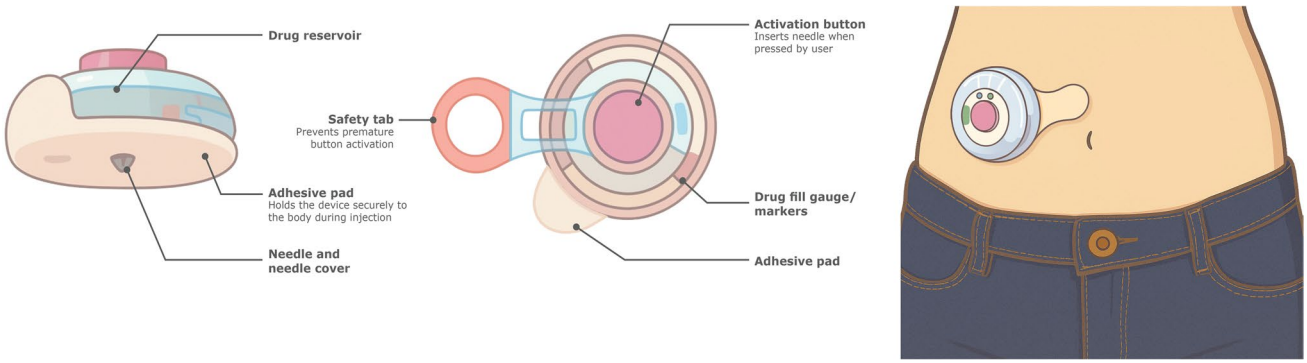

Fig. 2 Schematic diagram of a wearable subcutaneous injector for large-volume biologics. The illustration shows key structural components including the drug reservoir, activation mechanism, adhesive interface, and safety features that enable at-home wearable delivery of high-viscosity and/or high-volume biological formulations

efficacy and enhancing patient comfort, safety, and adherence to treatment regimens [69–72].

Fluid Dynamics in SC Administration

Flow rate directly impacts both therapeutic absorption and patient tolerability. Infusion rates exceeding 1 ml/min have been associated with increased discomfort and reduced bioavailability, as the SC tissue has limited capacity to accommodate rapid fluid expansion [58, 62, 73]. Conversely, slower, controlled delivery supports uniform dispersion of the drug, facilitating more favourable pharmacokinetics and improved patient experience [63].

Viscosity plays a critical role in determining the injection force required [74]. High-viscosity formulations, common amongst monoclonal antibodies and other large-molecule biologics, demand increased mechanical force, which often exceeds the capabilities of conventional spring-based devices [75]. Unregulated injection of such formulations may result in fluctuating flow patterns, user discomfort, and inconsistent dosing [76, 77].

Modern OBDDs address these challenges through electromechanical actuation and pressure modulation technologies, which enable real-time control of infusion dynamics [44]. Devices equipped with programmable actuators and integrated pressure sensors can adjust flow profiles in response to feedback, maintaining consistent pressure across the injection period [65, 78]. This approach mitigates flow variability, minimises injection site pain and leakage, and ensures complete dose delivery.

Delivery duration is equally influential. It is shaped by a combination of formulation characteristics (e.g. viscosity), tissue resistance, and actuator performance [79]. Extended-duration infusions in OBDD systems, when properly modulated, reduce mechanical stress on tissue and enhance drug dispersion. Devices incorporating variable-speed actuators and adaptive algorithms are now capable of tailoring infusion profiles to real-time physiological feedback, further improving therapeutic reliability [23, 80].

Engineering Innovations in Flow Modulation

Recent advances in microelectromechanical systems (MEMS) are enabling fine-tuned control of drug delivery kinetics. MEMS-based technologies integrate micro-actuators, sensors, and intelligent control circuitry to regulate flow rate, pressure, and infusion timing dynamically [44, 64, 81]. This allows systems to respond to fluctuations in drug viscosity or tissue resistance, optimising absorption whilst minimising discomfort. Such precision also supports prolonged delivery regimens, enhancing therapeutic outcomes and reducing injection site trauma [77].

Tissue Resistance and Enzymatic Modulation

A major physiological barrier to high-volume SC delivery is the limited capacity and permeability of the SC tissue space [82]. The extracellular matrix (ECM) in this region is rich in structural proteins such as collagen, elastin, and glycosaminoglycans, especially hyaluronic acid, which confer tensile strength but impede fluid dispersion [71]. Under normal physiological conditions, the SC space tolerates only 1–2 ml per injection site without causing significant discomfort or morphological stress [9, 62].

To overcome these anatomical constraints, co-formulation with recombinant human hyaluronidase (rHuPH20) has emerged as a clinically validated strategy [9, 83]. By enzymatically depolymerising hyaluronic acid, rHuPH20 transiently increases ECM permeability, enabling more efficient absorption of large fluid volumes [77, 84, 85]. This approach has been successfully implemented in several commercial therapies. For example, the HYQVIA® formulation (immunoglobulin G with rHuPH20) achieves approximately 93.3% of the bioavailability of its IV counterpart [86, 87]. Similar benefits have been observed in SC formulations of trastuzumab (Herceptin Hylecta®), rituximab (Rituxan Hycela®), and daratumumab (Darzalex Faspro®), which all allow for fixed-dose delivery with reduced infusion times [88–90].

Hyaluronidase thus plays a critical role in expanding the feasibility of SC delivery. By enabling volumes exceeding 10 ml to be infused subcutaneously, it supports the transition of high-dose biological therapies from hospital settings to patient-centric, at-home administration models [83]. Its integration with wearable OBDDs further enhances the clinical potential of these platforms, bridging mechanical innovation with physiological compatibility.

Building on recent work by, advancements in formulation science, which integrates nanotechnology, smart biomaterials, and precision engineering, are being designed to enhance therapeutic efficacy, improve patient compliance, and enable disease-specific targeting. Notably, the convergence of nanocarriers, bioresponsive polymers, and AI-optimised delivery systems is transforming SC drug administration. These innovations support prolonged drug release, targeted delivery, and reduced side effects across diverse therapeutic areas from chronic diseases to cancer and vaccines, ushering in a new era of personalised, minimally invasive treatment strategies.

Needle Mechanisms

The needle interface that encompasses gauge, length, bevel geometry, and insertion mechanism is a critical determinant of both the mechanical efficiency and user experience in SC drug delivery systems. This interface governs not only the physical execution of drug administration but also the

patient's perception of comfort, safety, and confidence, which in turn affects long-term adherence, particularly in home-use biologics infusions [69, 91].

Needle gauge (diameter) directly impacts flow dynamics. Larger bore needles (21G–25G) accommodate high-viscosity formulations by reducing flow resistance, enabling faster injection rates and lower required forces. However, they are frequently associated with increased pain and local trauma due to tissue disruption [92]. Conversely, finer gauges (27G–30G) offer enhanced patient comfort and are better tolerated, but their smaller lumens significantly increase hydraulic resistance. Thus, elevated backpressure, particularly in viscous formulations (e.g. > 15–30 cP), can necessitate injection forces exceeding 20 N or delivery pressures over 10–15 psi to maintain target flow rates (e.g. 1 ml/min) [93]. Insufficient compensation for this resistance can result in dose delivery delays, device fatigue, or incomplete administration [69].

Needle length is another critical parameter to consider [91]. Optimal SC deposition typically occurs with needle lengths ≤ 5 mm, reducing the risk of unintentional IM administration, especially in lean individuals or those with limited adipose tissue [94, 95]. Modern SC delivery devices are integrating automated insertion mechanisms, including motorised or spring-actuated systems, to ensure consistent and user-independent penetration depth [96]. These mechanisms will not only reduce manual error but also improve reliability across diverse patient anatomies and use scenarios [97]. Figure 3 shows four primary types of parenteral injections: intradermal (ID), intravenous (IV), subcutaneous (SC), and intramuscular (IM). The injection type is based on the anatomical depth of drug delivery and insertion angle when using a traditional syringe and needle. Although depicted here using standard needle–syringe assemblies, modern OBDD systems are designed with needle gauges and lengths optimised to reach the SC tissue layer directly, without requiring angulation during insertion.

Automation enables refined control over needle insertion and retraction speed, parameters increasingly recognised as important to reducing patient discomfort and mechanical variability. Such precision is particularly valuable in self-administered therapies and amongst users with limited dexterity or needle-related anxiety [77, 98, 99].

To further enhance safety and compliance with regulatory expectations, next-generation SC platforms incorporate integrated features such as needle shielding, automatic

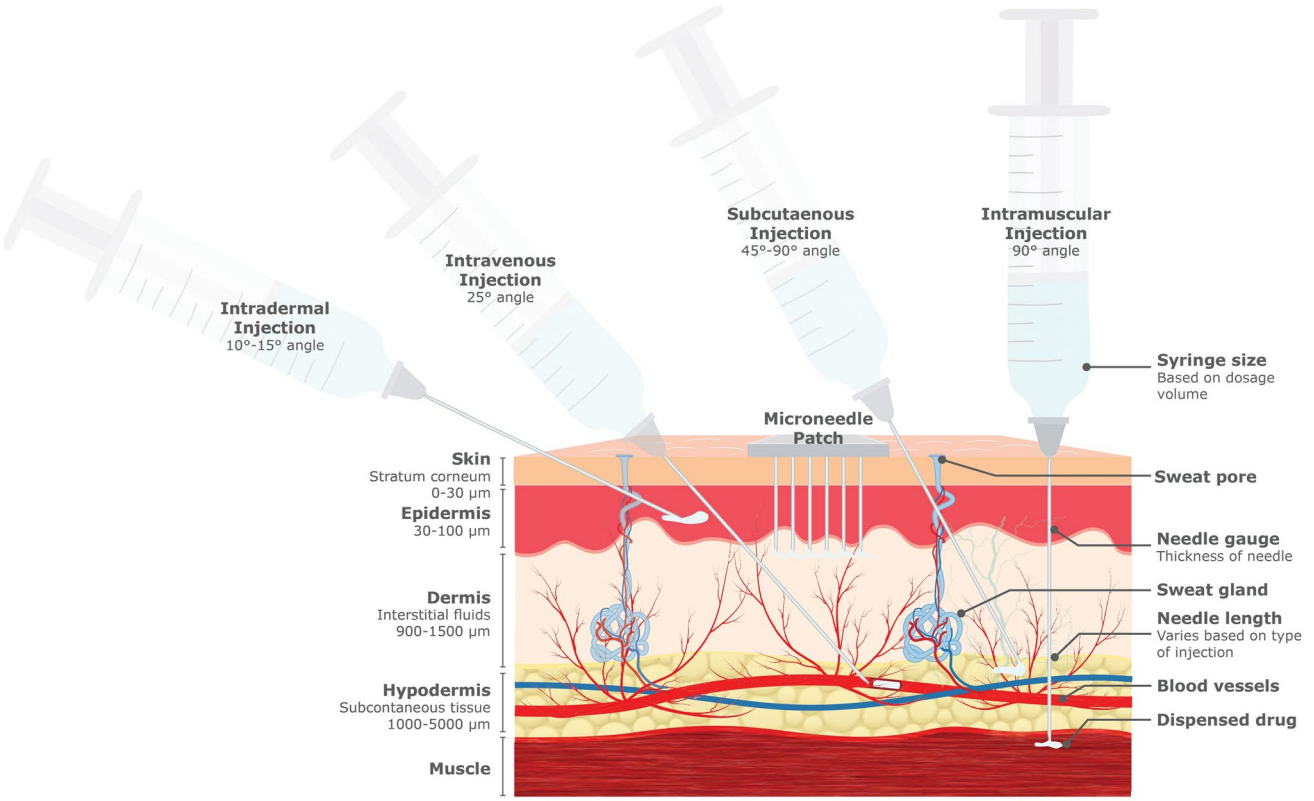

Fig. 3 Types of injections based on anatomical depth and insertion method. Schematic cross-section of the human skin depicting typical needle angles, depths, and insertion layers for intradermal (ID), subcutaneous (SC), and intramuscular (IM) injections. Intradermal injections target the dermis at a shallow angle (10°–15°), whilst SC injections are administered at 45°–90°, penetrating into the hypodermis or subcutaneous fat layer. IM injections reach deeper into muscle tissue at a 90° angle

retraction, and real-time leak detection. Needle shielding minimises accidental needlestick injuries and improves device disposal practices, whilst leak detection systems confirm complete dose delivery, flagging under-delivery events or device malfunctions [100]. Together, these innovations enhance both the technical robustness and patient acceptability of SC delivery systems.

Adaptive and Feedback-Controlled Delivery Platforms

Building upon advances in needle mechanism design that have enabled reliable SC access, recent developments in OBDD devices have shifted toward systems capable of real-time adaptation to patient-specific physiological conditions and formulation-dependent variables. These next-generation OBDDs employ closed-loop feedback control architectures that continuously monitor injection dynamics, such as tissue backpressure, flow rate, and resistance, particularly relevant for high-viscosity or large-volume biologics [65, 101].

Sensor-derived data are processed via embedded microcontrollers, which execute real-time control algorithms to detect deviations from predefined infusion parameters [101]. In response, actuator characteristics, including applied driving force and injection duration, are dynamically modulated to sustain controlled and safe drug administration profiles [96]. This adaptive functionality ensures the infusion remains within therapeutic delivery specifications despite variability in tissue compliance or fluid rheology [102]. Central to this control paradigm are miniaturised microelectromechanical systems (MEMS)-based actuators that enable precise modulation of force and flow [72]. In contrast to conventional spring-based devices that deliver fixed-force profiles and are susceptible to transient pressure spikes, adaptive actuators facilitate smooth initiation and sustained injection flow. This results in enhanced dosing precision and a reduction in both injection site pain and mechanical trauma, which are critical for the SC delivery of large volumes or viscous biologics [102].

Beyond flow control, these adaptive feedback systems offer design advantages including miniaturisation, component modularity, and support for reusable actuation modules paired with disposable drug reservoirs. These features not only contribute to sustainability but also improve patient convenience, particularly in home-based or ambulatory care settings. Importantly, such platforms hold potential for self-adjusting performance in response to interpatient variability in SC tissue characteristics, thereby enhancing safety and adherence across diverse patient populations [103].

The integration of intelligent feedback systems is especially vital as SC delivery expands into therapeutic areas requiring administration of volumes greater than the 20 ml range. Closed-loop control enables real-time compensation for increases in tissue resistance, ensuring infusion feasibility and minimising patient discomfort.

To illustrate the current landscape, Table 3 summarises the range of OBDD configurations either in use or under development. Devices are categorised by their core delivery mechanism: spring-based mechanical drives, electromechanical motor-driven systems, pressure-actuated devices, and platforms. Devices in Table 3 are representative commercial or investigational examples, with drug volume capacities ranging from small-volume formulations (~3 ml) [104, 105] to high-volume biologics up to 20 ml [38].

Clinical Applications by Therapeutic Area

OBDD systems are emerging as critical enablers of large-volume and/or high-viscosity subcutaneous biological delivery, addressing unmet clinical needs across a growing range of therapeutic areas, including oncology, autoimmune disorders, haematological conditions, and rare diseases. Several devices with SC delivery volumes ranging from 2.4 to 20.0

Table 3 Commercial and late-stage On-Body Drug Delivery Devices (OBDDs) approved or in development in the U.S.A. and Europe

Product Name	Company	Drug/Active Substance	Drive Mechanism	Delivery Time	Status/Approval
Neulasta® Onpro® [53]	Amgen	Pegfilgrastim	Gas pressure (chemical)	5–7 min	FDA approved
BD Libertas™ [106]	BD	Undisclosed (platform)	Spring-based mechanical	~5–10 min	CE-marked
SmartDose® [104]	West Pharmaceutical Services	Undisclosed platform	Electromechanical	20–30 min	Commercialised (FDA path)
Enable enFuse® [38]	Enable Injections	Various (platform)	Pressure based	Over 30 min	Clinical use/CE-marked
YpsoDose® [107]	Ypsomed	Undisclosed (platform)	Electromechanical	Up to 30 min	CE marked
Subcuject® [108]	Subcuject	Undisclosed (platform)	Osmotic drive	~10 min	In development
MiniMed® 780G [105]	Medtronic	Insulin	Motorised pump	Programmable/real time	FDA approved

Listed systems vary in drive mechanism, delivery duration, and regulatory status

ml have received regulatory approval or are under review [11, 109].

Oncology

Monoclonal antibodies (mAbs) are biologics therapies widely used in the treatment of various cancers [110]. Their design allows them to bind specifically to antigens expressed on cancer cells, which enables targeted intervention with minimised impact on surrounding healthy tissue. The primary use of mAbs is to treat cancer through IV infusions in clinical settings, where patients are closely monitored for safety due to the risk of infusion-related reactions. However, with the development of SC formulations, a limited number of SC mAb therapies can now be administered at home either by healthcare professionals or through patient self-injection, offering greater convenience for selected low-risk cases [15, 18, 55, 111]. Notable SC mAb therapies, such as trastuzumab, the trastuzumab/pertuzumab combination, and daratumumab, which are used for HER2-positive breast cancer and multiple myeloma, have demonstrated pharmacokinetics and clinical efficacy comparable to those achieved with IV infusion [112–114]. These studies also show that SC delivery improves patient convenience, shortens administration time, and reduces healthcare resource use, making it a favourable alternative in suitable oncology settings.

Immunology

In immunological disorders, OBDDs support sustained SC delivery of biologics for chronic diseases such as rheumatoid arthritis, psoriasis, Crohn's disease, and ulcerative colitis. Skyrizi® (risankizumab) Stelara® (ustekinumab), approved for Crohn's disease and ulcerative colitis, mark a significant advance toward patient-friendly SC regimens [115, 116]. In addition, the use of biological-device combinations such as SC Humira® (adalimumab) and SC Enbrel® (etanercept) has established a precedent for auto-injectors, enhancing convenience and promoting at-home self-administration [117, 118].

Haematology and Rare Diseases

OBDDs have proven critical in the management of haematological and rare disorders, particularly where large-volume or frequent dosing is required. Empaveli® (pegcetacoplan), indicated for paroxysmal nocturnal hemoglobinuria (PNH), is administered in a 20-ml dose via an OBDD, enabling self-treatment at home and significantly improving haemoglobin levels whilst reducing transfusion dependency [119, 120].

Cardiovascular and Endocrine Applications

Emerging therapeutic areas for OBDDs include cardiovascular disease and hormone therapy. Repatha® (evolocumab), for example, delivers a 3.5 ml monthly dose to lower lipid levels, demonstrating effective long-term cardiovascular risk management [121].

Supportive Care

Onpro®, one of the earliest commercialised OBDDs, automates SC delivery of Neulasta® (pegfilgrastim) following chemotherapy. It is worn on the upper arm or abdomen and delivers a single SC dose approximately 27 h after application, avoiding the need for a patient to return to the clinic the day after chemotherapy [18]. Real-world evidence supports improved adherence and reduced hospital resource burden through its use. Its clinical success laid the groundwork for future innovations in SC biological administration.

Product Ergonomics, Usability, and Risk Management

The development of wearable OBDDs demands a comprehensive, lifecycle-driven approach that balances engineering precision with regulatory compliance. Optimising product ergonomics, usability, and risk management is essential when integrating various components within patient-operated devices, which ensures both user safety and regulatory adherence [65]. By aligning with the Essential Drug Delivery Output (EDDO) validation [122], encompassing human-centred design, systematic risk management, and post-market surveillance, manufacturers can deliver wearable technologies that are not only innovative but also safe, dependable, and broadly accessible.

Safety Risks and Failure Modes

Wearable OBDDs operate in diverse, often unsupervised settings, exposing them to various safety and reliability risks. Key device-related concerns include needlestick injuries from failed or incomplete automatic retraction, blocked flow pathways, mechanical malfunctions, and power failures interrupting therapy [29]. Equally significant are user-related issues, such as incorrect placement, early detachment, or misinterpretation of interface cues, which can lead to partial dosing or adverse outcomes [123]. These risks underscore the need for early integration of human factors engineering to anticipate user errors and embed robust mitigation strategies that improve overall safety and performance.

Essential Drug Delivery Outputs (EDDOs)

According to the draft guidance by the U.S. Food and Drug Administration (FDA) EDDOs represent the critical system-level outputs required for consistent, safe, and effective drug delivery, regardless of user behaviour. These parameters must be rigorously verified and validated under real-world conditions. For wearable OBDDs, key EDDOs include flow rate accuracy, dosing duration, needle deployment and retraction reliability, skin adhesion strength, and actuation force thresholds. Manufacturers must clearly define these outputs, implement appropriate safeguards (e.g. occlusion detection, automatic retraction), and demonstrate performance via comprehensive stress testing. Following ISO 14971-compliant risk management protocols [124, 125] ensures thorough risk identification, assessment, control, and traceability throughout the medical device lifecycle. The authors affirm that documenting EDDOs and associated mitigation strategies not only strengthens regulatory submissions but also supports effective root cause analysis during post-market investigations, which ultimately protects patient safety and manufacturer integrity.

Ergonomics and Patient Usability

Human factors engineering is critical to the successful deployment of wearable OBDDs, where ease of use directly correlates with adherence, safety, and therapeutic efficacy. Ergonomic design principles must address the spectrum of user capabilities and preferences, minimising physical exertion and cognitive demands throughout the use cycle. Andre, Mohr [123] argue that the effective use of an OBDD is governed by its safety and can be effectively used by patients, caregivers, and clinics regardless of training.

In alignment with the U.S. FDA's guidance on human factors engineering, usability should be systematically integrated from the earliest stages of device development. This includes iterative prototyping, user testing, and failure mode analysis across diverse demographic cohorts, including older adults, individuals with limited dexterity, and users with cognitive impairments. Intuitive interfaces that provide multimodal cues (visual, auditory, tactile) during critical operations, such as activation, dose administration, and delivery confirmation, can significantly reduce use errors [126].

To ensure reliability under real-world conditions, usability testing must replicate environmental variability and psychological stressors typical of home and community-based settings. Validated performance under these conditions increases user confidence and supports sustained self-management. As such, wearable systems that integrate ergonomic sophistication with engineering resilience represent a foundational element in the shift toward decentralised therapeutic models, enabling patients to administer complex treatments safely and autonomously [123].

Regulatory Overview in the USA and European Union

Wearable OBDDs represent a distinct category within the regulatory landscape, as they integrate drug, biological, and device components into a single therapeutic system. As defined by the U.S. FDA [127], these are classified as combination products since their primary mode of action cannot be attributed exclusively to either the drug or the device. As a result, OBDDs must meet the regulatory standards applicable to both pharmaceuticals and medical devices [126]. The development and approval of these wearable systems, particularly within the U.S. and European Union, require navigation through complex, region-specific regulatory frameworks. These frameworks differ notably in terms of product classification, submission processes, and post-market responsibilities, reflecting the need for coordinated compliance across disciplines [26].

Device Classification and Premarket Submission

The FDA classifies medical devices into Classes I, II, and III, with wearable OBDDs typically categorised as Class II or Class III depending on their risk profile [128]. Devices delivering biologicals often fall into Class III, requiring a Premarket Approval (PMA) process, demanding clinical evidence demonstrating safety and efficacy. Devices delivering well-characterised drugs may seek 510(k) clearance by demonstrating substantial equivalence to an existing legally marketed device. The 510(k) clearance process refers to a premarket submission made to the FDA to demonstrate that a new medical device is substantially equivalent to a legally marketed predicate device [129].

In the European Union, drug–device combinations (DDC) are regulated under Regulation (EU) 2017/745 on medical devices (MDR) and corresponding medicinal product legislation. Devices containing a medicinal substance that acts in an ancillary manner are automatically classified as Class III under Rule 14 of MDR Annex VIII. Notified Bodies (NBs), designated under the MDR, assess conformity and must consult with national competent authorities (NCAs) or the European Medicines Agency (EMA) regarding the drug component.

For DDCs regulated primarily as medicinal products, the Common Technical Document (CTD) format, established by the International Council for Harmonization (ICH), is required for marketing authorisation applications in various regions. Article 117 of the MDR further mandates that the device component comply with General Safety and Performance Requirements (GSPRs), demonstrated by a

Declaration of Conformity, NB certificate, or NB opinion [130].

Integrating Human Factors and Regulatory Compliance

Medical device manufacturers must comply with both device-specific quality system regulations (21 CFR Part 820) and pharmaceutical current Good Manufacturing Practices (cGMP) (21 CFR Parts 210 and 211). The FDA's Final Rule for Combination Products (21 CFR Part 4) mandates the integration of these regulatory frameworks into a unified quality management system (QMS) [131]. Furthermore, human factors engineering (HFE) and usability studies, aligned with ISO 62366 and ISO 14971, are critical in demonstrating that devices can be used safely by patients across diverse demographic groups without direct clinical supervision [123].

Software and Connectivity Requirements

Many wearable OBDDs incorporate software-driven functionality. Software elements may qualify as Software as a Medical Device (SaMD) if they independently facilitate medical decisions [132, 133]. All software must comply with FDA cybersecurity, risk mitigation, and interoperability requirements. Post-market software updates must demonstrate that modifications do not compromise device safety or performance.

The European Union (EU) regulatory framework for software in medical devices, including SaMD and wearable OBDDs, is governed by the Medical Device Regulation (EU) 2017/745 (MDR). This regulation emphasises software validation, cybersecurity, post-market surveillance, and interoperability. Connectivity and digital updates are tightly regulated under the concepts of risk-based classification, software lifecycle requirements, and performance equivalency.

Post-Market Surveillance and Regulatory Oversight

Post-market surveillance (PMS) is a critical and legally mandated element in the lifecycle management of drug–OBDD combinations. It ensures the ongoing assessment of safety, effectiveness, and usability in real-world settings, where decentralised use introduces variability that may not be captured during premarket validation. As such, PMS functions both as a scientific feedback mechanism and a regulatory requirement aimed at sustaining therapeutic integrity and minimising risk throughout the product lifecycle.

In the USA, PMS activities are governed by the FDA and include structured adverse event reporting through the Manufacturer and User Facility Device Experience (MAUDE) database [124]. This repository collects data on device malfunctions, safety concerns, and patient injuries from manufacturers, healthcare professionals, importers, and patients, facilitating early detection of systemic issues. Data mined from MAUDE supports regulatory decision-making, including labelling modifications, safety communications, and product recalls.

Complementing public databases, manufacturers are expected to implement comprehensive internal monitoring systems. These may encompass service logs, customer feedback mechanisms, trending analyses, and compliance with the Unique Device Identification (UDI) system, which enhances traceability, recall efficiency, and transparency in the supply chain.

Internationally, the European Medical Device Regulation (MDR) imposes even more detailed PMS obligations [134]. Manufacturers must conduct Post-Market Clinical Follow-Up (PMCF) studies, submit Periodic Safety Update Reports (PSURs), and adhere to vigilance reporting protocols. These requirements are designed to continually evaluate the benefit-risk balance and capture emerging risks in the post-commercialisation phase. Furthermore, any significant modifications to device design or manufacturing processes, particularly those influencing the drug constituent or primary mode of action, require reassessment by the designated Notified Body (NB), potentially triggering updated conformity assessments and scientific consultations [135, 136].

Together, these layered surveillance mechanisms spanning internal quality systems, national registries, and international regulatory mandates form a comprehensive oversight framework. This framework not only facilitates early intervention and adaptive risk management but also reinforces public trust and clinician confidence in the long-term deployment of wearable OBDDs.

Manufacturing, Supply Chain, and Cost Considerations

As OBDDs gain broader clinical adoption, the industry focus has shifted from innovation and design to the practical challenges of scalable manufacturing, cost containment, and environmental sustainability [137]. These systems, designed to deliver high-viscosity biologics over prolonged periods, offer clear clinical and economic advantages by supporting home-based care and promoting long-term adherence. However, realising these benefits at scale necessitates overcoming significant technical, logistical, and ecological hurdles.

Complex Assembly and Manufacturing Requirements

OBDDs integrate multiple subsystems comprising drug reservoirs, electromechanical actuators, sensors, microprocessors, batteries, and wireless modules, all within compact, biocompatible enclosures. The manufacturing process,

therefore, demands micro-scale precision in aligning, assembling, and bonding these components [137]. Sterilisation constraints and material compatibility further complicate production workflows [138]. In contrast to traditional formats, such as prefilled syringes, OBDDs present a higher manufacturing complexity and cost profile. Key cost drivers include specialty materials (e.g. drug-contact-safe polymers, silicone adhesives), embedded electronics (e.g. printed circuit boards, bluetooth modules), and high-precision assembly methods (e.g. ultrasonic welding, overmolding).

To meet production volume and quality demands, many pharmaceutical developers outsource manufacturing to contract manufacturing organizations (CMOs) with established expertise in medical device fabrication and cleanroom assembly. Whilst this strategy can accelerate time to market, it also introduces supply chain vulnerabilities, particularly amid ongoing global shortages of semiconductors and medical-grade polymers.

Economic Value and Reimbursement Considerations

Despite high upfront development and manufacturing costs, OBDDs have demonstrated favourable health-economic performance when evaluated across the full spectrum of care [139]. Published studies underscore their contribution to reducing acute care visits, lowering hospital readmissions, and improving control of chronic conditions [22, 140]. As drug delivery evolves toward autonomous and personalised paradigms, OBDDs help mitigate systemic pressures on healthcare systems, particularly for long-duration or maintenance therapies.

To support reimbursement and payer adoption, manufacturers increasingly employ pharmacoeconomic modelling, including cost-effectiveness analyses and budget impact assessments, to quantify long-term value [141, 142]. These models help stakeholders assess whether the higher initial costs of OBDDs are offset by downstream healthcare savings, improved adherence, and better clinical outcomes. Demonstrating cost-effectiveness, or value for money, has become essential in securing favourable pricing and access decisions [143].

Environmental Sustainability and Eco-Design Challenges

The environmental footprint of single-use OBDDs is a growing concern [144]. Disposal of batteries, electronic components, and adhesive-backed housings contributes to substantial landfill waste. Although disposability ensures sterility and user convenience, it exacerbates challenges related to plastic accumulation and electronic waste. Industry responses include early-stage exploration of modular, recyclable, or semi-reusable formats, which aim to reduce environmental impact but face barriers involving cleaning validation, patient compliance, and regulatory approval for device reprocessing.

To address these concerns, OBDD developers and manufacturers are adopting modular configurations that minimise environmental burden throughout the product life cycle [145]. Such solutions facilitate cost-efficiency and lifecycle optimisation, aligning with broader healthcare goals that readily adapt to different patient populations, therapeutic areas, or volume/dose needs. A key strategy is the modular separation of disposable and reusable elements, allowing for simpler disassembly and recycling, and reducing contamination between hazardous and non-hazardous materials. Additionally, take-back programmes facilitate the safe return and responsible disposal of used devices, aligning with regulatory mandates and corporate sustainability goals.

Other innovations include the use of low-power electronics and the development of biodegradable battery technologies, which aim to reduce energy consumption and mitigate long-term ecological risks [146, 147]. These initiatives reflect a broader shift toward sustainability in medical device manufacturing.

Semi-reusable OBDDs where electronic modules are retained and paired with disposable drug cartridges are also under investigation [23]. Whilst these platforms offer a compelling environmental benefit, they raise new challenges in terms of design complexity, reusability validation, and patient training.

Scaling for the Future

The successful scaling of OBDD production will require careful alignment of technological sophistication, cost-effectiveness, and sustainability. Strategic partnerships with CMOs, investment in manufacturing automation, and the integration of circular design principles will be essential for delivering next-generation systems that meet clinical needs whilst supporting economic and environmental viability [148].

Market Dynamics and Innovation in Wearable OBDD Systems

The accelerating adoption of wearable on-body drug delivery (OBDD) systems is reshaping the commercial and technological landscape of drug–device combination products. This growth is driven by macro-level forces, including the global rise in chronic diseases, necessitating long-term administration of complex biologics that are increasingly suitable for subcutaneous (SC) self-delivery in non-clinical settings [149]. Patients and providers alike are prioritising convenience and autonomy, which in turn alleviates pressure on the healthcare infrastructure.

Key technological enablers include advances in formulation science that allow high-viscosity and large-volume biologics to be delivered SC rather than intravenously [19], and the integration of microfluidic and digital health platforms that enable smarter, programmable, and more patient-centric therapies. The regulatory landscape has also matured, with harmonised pathways for combination products supporting faster and more predictable commercialisation.

From a competitive perspective, established pharmaceutical leaders, such as Amgen (Neulasta® Onpro®), Roche (Phesgo®), and Janssen (Darzalex Faspro®), have demonstrated successful execution in bringing wearable biological therapies to market [150]. Simultaneously, device-centric medtech innovators, such as Enable Injections, Subcuject, and Sorrel Medical, are advancing modular, platform-based technologies that enable scalable production, customisation, and cross-licensing [39, 40, 151].

Strategic alliances and co-development models have emerged as a hallmark of this sector. For example, the partnership between Amgen and West Pharmaceutical Services illustrates how integrated drug–device development can yield commercially viable and regulatory approved products [53].

Looking ahead, the wearable biologics market is projected to grow at a compound annual growth rate (CAGR) of 11–15% through 2028 [150], with applications expanding into gene therapies, RNA biologics, and high-concentration monoclonal antibodies [93, 152]. As this therapeutic footprint broadens into neurology, endocrinology, and infectious diseases, critical challenges such as temperature sensitivity, adaptive dosing, and programmable release must be addressed through cross-sector innovation.

Opportunities for Innovation with Biosimilars Through Drug Delivery Devices

In the competitive biosimilars market, drug delivery technologies have become a key frontier for differentiation beyond molecular equivalence. Although regulatory standards require analytical and clinical comparability to reference biologics, biosimilar developers are increasingly leveraging advanced delivery systems to enhance therapeutic value and market positioning. Innovative delivery devices that support real-world effectiveness are repositioning biosimilars as value-added alternatives even after originator patent expiry. In price-driven markets, delivery innovations offer a means of distinction, facilitating entry into underserved niches and improving access through favourable health technology assessments. Strategic partnerships between pharmaceutical and medtech companies are central to this innovation. These collaborations integrate engineering and human factors design into biosimilar platforms. Spooner and Simpson [153] emphasise that drug delivery innovation now rivals molecular composition in shaping biosimilar success. Their work advocates for a multidimensional approach to product design, integrating pharmacological, technological, and behavioural factors. Consequently, drug delivery innovation is not a peripheral consideration but a core strategic element in biosimilar development.

Discussion

The emergence of wearable OBDDs marks a pivotal advancement in the administration of complex biologics. However, their translation from innovation to standard of care is contingent upon overcoming several persistent challenges. Key points amongst these are optimising device performance in real-world environments, ensuring inclusivity across diverse patient populations, and navigating evolving global regulatory landscapes.

From a product engineering perspective, the reliable SC administration of large-volume, high-viscosity biologics remains a complex undertaking. Achieving consistent flow rates and complete dose delivery for large-volume and/or high-viscosity SC biologics, particularly in the presence of variable tissue compliance and ambient conditions, calls for the continued refinement of drive mechanisms, needle systems, and adaptive control algorithms. The success of next-generation OBDDs will hinge on integrating precision engineering with wearable ergonomics by balancing miniaturisation, automation, and patient comfort without compromising reliability.

Patient centricity must be a central design pillar. Despite significant advances in usability, barriers such as limited dexterity, sensory impairments, and cognitive load persist. Device design must evolve toward universal accessibility, emphasising intuitive interfaces, multimodal feedback, and built-in safeguards to mitigate administration errors. Additionally, patient trust hinges on consistent performance, robust safety features, and transparency in functionality, especially in unsupervised, home-based use scenarios.

On a systemic level, regulatory harmonisation remains fragmented. The duality of OBDDs as drug–device combinations subjects them to complex, often regionally divergent approval processes. Unified global frameworks that streamline classification, human factors validation, and post-market surveillance are urgently needed to accelerate access and ensure consistency in safety standards. Moreover, reimbursement systems must evolve to recognise the long-term value proposition of OBDDs in reducing hospital burden and improving adherence.

Looking ahead, two technological domains—closed-loop systems and programmable delivery systems—are poised to significantly reshape the next generation of wearable biological delivery. These innovations integrate responsive control

mechanisms and advanced materials to enable adaptive, personalised, and sustained administration of biologics. The following subsections explore these emerging approaches in greater detail.

Closed-Loop Systems

Closed-loop theragnostic systems represent an emerging frontier in wearable drug delivery, merging diagnostic sensing with automated therapeutic response to enable real-time, adaptive treatment. These systems integrate continuous biomarker monitoring (e.g. glucose, lactate, cortisol) with feedback-controlled drug release, thereby personalising therapeutic regimens based on dynamic physiological signals [154]. This convergence of monitoring and actuation supports the broader goal of precision medicine and offers a pathway toward truly patient-centric, self-regulating care platforms.

Recent advances in biosensors, smart hydrogels, and microfluidic integration have enabled the development of wearable platforms that not only track disease-relevant biomarkers but also modulate dosing in real time. For instance, glucose-responsive microneedle arrays have been shown to autonomously release insulin or glucagon in response to glycaemic fluctuations, maintaining tighter glycaemic control without external intervention [30]. Microneedles (MNs) are minimally invasive, micron-scale projections capable of painlessly breaching the stratum corneum (outermost layer of the skin) to enable transdermal delivery of therapeutics or access to interstitial fluid [32, 155, 156]. MNs have evolved into versatile wearable platforms for controlled, user-friendly drug administration [31, 156].

Whilst many of these closed-loop platforms remain in early-stage research or preclinical testing, their potential to reduce therapeutic lag, improve adherence, and mitigate risks associated with over- or under-dosing is substantial [157]. From a market perspective, closed-loop systems are positioned at the intersection of digital health, wearable technologies, and biological therapy, offering a compelling value proposition for managing chronic conditions such as diabetes, autoimmune diseases, and cancer. Continued development of robust, biocompatible sensors, integration with wireless communication modules, and regulatory frameworks for adaptive dosing algorithms will be essential to the clinical realisation of these systems. Nonetheless, the evolution of wearable OBDD technologies into intelligent, self-regulating platforms underscores a key innovation trajectory in the field [102].

Programmable Delivery Systems

Polymeric drug delivery systems capable of programmable or on-demand release are an emerging class of technologies that offer novel strategies for subcutaneous (SC) administration of biologics [158, 159]. These systems leverage physicochemical triggers such as pH, temperature, or enzymatic activity to achieve spatially and temporally controlled release. Advances in fabrication techniques, including microfluidics, electrospraying, and solvent evaporation, have enabled the production of polymeric microparticles and hydrogels with finely tunable release kinetics. These systems enhance drug stability, improve bioavailability, and offer potential for reducing dosing frequency and systemic toxicity, particularly for biologics requiring subcutaneous administration [160, 161]. Notable examples include dissolvable microneedles for vaccine or insulin delivery and hydrogel-based depots under investigation for monoclonal antibody release [162–164].

Despite their promise, current biomaterial-based systems face limitations for integration with wearable OBDD platforms. These include challenges in real-time modulation of dosing, limited reusability, difficulties in controlling precise bolus delivery, and protein stability during encapsulation and release. Moreover, the fixed nature of depot-based release can be suboptimal for therapies requiring flexible, patient-controlled timing or frequent dose adjustments [158, 159].

Whilst these systems are not presently used in commercially approved OBDDs, they represent a complementary direction in the advancement of SC biological delivery and may be increasingly considered in hybrid or next-generation wearable formats.

Conclusion

The future of OBDDs lies at the intersection of biomedical engineering, digital health, and personalised medicine. When guided by inclusive design and validated through real-world evidence, these platforms can democratise biological access and redefine the patient experience. As therapeutic applications broaden across neurology, endocrinology, and infectious disease, particularly for large-volume subcutaneous biologics, device development must address increasingly complex demands, such as temperature-sensitive formulations, adaptive dosing strategies, and programmable delivery systems tailored to novel biologics. Meeting these challenges will require coordinated efforts across sectors, drawing on expertise from industrial design, engineering, clinical practice, regulatory science, and patient engagement. With thoughtful innovation and collaborative stewardship, wearable injectors are well positioned to become central to the next era of equitable, patient-centred care.

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Declarations

Competing Interests The authors declare no competing interests.

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