Autoinjectors for large-volume subcutaneous drug delivery: a review of current research and future directions

Andreas Schneider, Reto Jost, Christoph Jordi & Jakob Lange

To cite this article: Andreas Schneider, Reto Jost, Christoph Jordi & Jakob Lange (2023): Autoinjectors for large-volume subcutaneous drug delivery: a review of current research and future directions, Expert Opinion on Drug Delivery, DOI: 10.1080/17425247.2023.2219891

To link to this article: https://doi.org/10.1080/17425247.2023.2219891

© 2023 The Author(s). Published by Informa UK Limited, trading as Taylor & Francis Group.

Published online: 04 Jun 2023.
Autoinjectors for large-volume subcutaneous drug delivery: a review of current research and future directions

Andreas Schneider, Reto Jost, Christoph Jordi and Jakob Lange

Ypsomed Delivery Systems, Ypsomed AG, Burgdorf, Switzerland

ABSTRACT

Introduction: The growing interest in subcutaneous delivery of larger single-dose volumes using handheld autoinjectors raises questions about the feasible upper limits for injection volume and rate. This review critically evaluates the literature on subcutaneous administration with dose volumes greater than 1.0 mL. In so doing, it examines how previous work has addressed limitations and considerations for designing and developing large-volume autoinjectors.

Areas covered: This article synthesizes 31 studies on large-volume subcutaneous delivery through a systematic review process and structures their findings based on three themes critical to developing large-volume autoinjectors: injection tolerability, suitability for self-administration, and pharmacokinetic equivalence with existing dosing options. This review highlights the answers provided by previous studies and identifies promising avenues for future research.

Expert opinion: This review finds that the literature supports the feasibility of delivering single large-dose subcutaneous volumes, providing a foundation for large-volume autoinjectors. Moreover, the review guides future research to address questions within and across themes critical to large-volume autoinjector development, helping to provide health-care professionals and patients with more effective and convenient dosing options.

ARTICLE HISTORY

Received 15 February 2023
Accepted 26 May 2023

KEYWORDS

autoinjectors; injection tolerability; device usability; self-administration; pharmacokinetic equivalence; literature review; large-volume dose; subcutaneous drug delivery

1. Introduction

Subcutaneous drug delivery has emerged as a viable and often preferred alternative to intravenous infusion of biologics, offering patients and health-care providers new home-based treatment options that improve treatment adherence, reduce the cost of therapy, and decrease health-care resource utilization [1–6]. Although subcutaneous delivery options advance patient-centered care, their development faces numerous challenges ranging from pharmacoekinetcis and efficacy to bioavailability, viscosity, stability, and the development of delivery devices for safe and effective home use [7,8]. It is, therefore, hardly surprising that the industry has shown great interest in handheld autoinjectors that allow patients and caregivers to administer medications safely and effectively [9–11]. Figure 1 illustrates the user steps of a ready-to-use prefilled handheld autoinjector with visual and audible feedback at the beginning and end of the injection. These spring-actuated mechanical devices, activated by pressing a button or pushing against the injection site, provide a needle safety function and deliver a predetermined fixed volume from a prefilled syringe within 10 to 20 s [12,13]. Following delivery into the subcutaneous tissue, liquid-formulated biologics accumulate locally as a fluid depot and traffic through the interstitial matrix into the lymphatic system, then into the bloodstream [14–16].

The availability of user-tested device platforms has broadened access to handheld autoinjectors for biologics in chronic diseases [10,17–20]. Tumor necrosis factors to mediate rheumatoid arthritis and other chronic debilitating diseases have pioneered home treatment with autoinjectors [20,21]. Today, subcutaneous dosing options exist for different drug modalities, such as bispecific antibodies [22] and small-interfering RNAs [23,24], and therapy areas, such as cardiovascular diseases and obesity [18,25–27], respiratory diseases [27,28], migraine [19,29–32], psoriasis [31,32], and rare diseases [10,19–22,33]. Handheld autoinjectors have become a preferred option for safe and effective self-administration of single doses and have been widely adopted as the standard for subcutaneous drug delivery [34,35].

The industry for a long time assumed the delivery of 1.0 mL in less than 10 to 15 s to be the feasible upper limit for handheld autoinjectors [31,36]. However, recent approvals of products with single-dose volumes up to 2.0 mL have demonstrated the successful delivery of larger volumes. Table 1 provides an overview of drugs marketed in the 2.25 mL single-dose prefilled syringe format. This has prompted pharmaceutical manufacturers to replace two sequential smaller dose-volumes with a single large-volume injection [47,48]. Moreover, research has shown that patients can safely and effectively complete large-volume injections lasting up to 30 s [36].
These recent advances have energized attempts to expand the feasible volume limit for handheld autoinjectors. Higher injection volumes not only reduce the frequency of injections and enhance patient preferences and therapy adherence [49–51] but also help establish subcutaneous dosing for new therapeutic areas and drug modalities that require larger single-dose volumes [2,52,53]. As such, the advent of handheld autoinjectors exceeding 2.0 mL capacity has garnered significant attention. Table 2 provides an overview of investigational large-volume autoinjectors that enable the delivery of single-dose volumes up to 10.0 mL. These devices could provide an alternative to more complex electromechanical large-volume wearable injectors that remain patched on the skin and slowly inject a single-dose volume over minutes if not hours [59–62]. However, there is uncertainty about the feasibility of the injection volume and the rate that can be achieved with high-volume handheld autoinjectors. Although previous literature reviews have summarized past work on large-volume subcutaneous injections [63–65], they have provided limited and somewhat fragmented insights into the feasibility of handheld autoinjectors for high-rate large-volume subcutaneous dosing. To address this gap, this article analyzes prior literature based on three themes to gain a more coherent understanding of large-volume autoinjectors: injection tolerability, suitability for self-administration, and pharmacokinetic equivalence with existing delivery options. These three themes are essential for the successful development and approval of novel large-volume autoinjectors.

Table 1. Approved products from the U.S. Food and Drug Administration and European Medicines Agency using 2.25 mL prefilled syringes, prefilled needle safety devices, and prefilled handheld autoinjectors.

<table>
<thead>
<tr>
<th>Product</th>
<th>Manufacturer</th>
<th>Presentation</th>
<th>Disease area</th>
<th>Dose</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>AJOVY (Fremanezumab)</td>
<td>Teva Pharma</td>
<td>AI, PFS</td>
<td>Migraine</td>
<td>225 mg/1.5 mL</td>
<td>[37]</td>
</tr>
<tr>
<td>COSENTYX (Secukinumab)</td>
<td>Novartis Pharma</td>
<td>AI, NSD</td>
<td>Inflammatory &amp; autoimmune</td>
<td>300 mg/2.0 mL</td>
<td>[38]</td>
</tr>
<tr>
<td>DUPIXENT (Dupilumab)</td>
<td>Sanofi/Regeneron</td>
<td>AI, NSD</td>
<td>Inflammatory &amp; autoimmune</td>
<td>300 mg/2.0 mL</td>
<td>[39]</td>
</tr>
<tr>
<td>LEQVIO (Inclisiran)</td>
<td>Novartis Pharma</td>
<td>PFS</td>
<td>Cardiovascular</td>
<td>284 mg/1.5 mL</td>
<td>[40]</td>
</tr>
<tr>
<td>PRALENT (Alirocumab)</td>
<td>Sanofi/Regeneron</td>
<td>AI</td>
<td>Cardiovascular</td>
<td>300 mg/2.0 mL</td>
<td>[41]</td>
</tr>
<tr>
<td>SILIQ (Brodalumab)</td>
<td>Valeant Pharmaceuticals</td>
<td>PFS</td>
<td>Inflammatory &amp; autoimmune</td>
<td>210 mg/1.5 mL</td>
<td>[42]</td>
</tr>
<tr>
<td>TEGSEDI (Inotersen)</td>
<td>Akcea/Ionis</td>
<td>PFS</td>
<td>Rare disease</td>
<td>284 mg/1.5 mL</td>
<td>[43]</td>
</tr>
<tr>
<td>TEZSPIRE (Tezepelumab)</td>
<td>AstraZeneca/Amgen</td>
<td>AI, NSD</td>
<td>Inflammatory &amp; autoimmune</td>
<td>210 mg/1.9 mL</td>
<td>[44]</td>
</tr>
<tr>
<td>TAKHZYRO (Lanadelumab)</td>
<td>Takeda Pharma</td>
<td>PFS</td>
<td>Rare disease</td>
<td>300 mg/2.0 mL</td>
<td>[45]</td>
</tr>
<tr>
<td>WAYLIVRA (Volanesorsen)</td>
<td>Akcea/Ionis</td>
<td>PFS</td>
<td>Rare disease</td>
<td>285 mg/1.5 mL</td>
<td>[46]</td>
</tr>
</tbody>
</table>

Note: Abbreviations. AI: autoinjector, PFS: prefilled syringe, NSD: needle safety device.
*Excludes large-volume dosing options administered using wearable large-volume injectors.
Table 2. An overview of investigational large-volume handheld autoinjectors with pre-filled syringes and cartridges exceeding 2.25 mL capacity.

<table>
<thead>
<tr>
<th>Product</th>
<th>Manufacturer</th>
<th>Handling principle</th>
<th>Primary packaging</th>
<th>User interface</th>
<th>Status</th>
<th>Maximum delivered volume [mL]</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aero uno</td>
<td>Kaleo (Richmond, VA, U.S.A)</td>
<td>Push-on-skin/2-step handling</td>
<td>Cartridge or prefilled syringe</td>
<td>Audible and visual cues (undisclosed)</td>
<td>Development</td>
<td>10.0</td>
<td>[54]</td>
</tr>
<tr>
<td>ARAI</td>
<td>Aktiv Pharma (Broomfield, CO, U.S.A)</td>
<td>Push-on-skin/2-step handling</td>
<td>Flexible, glass-free container</td>
<td>Undisclosed</td>
<td>Development</td>
<td>5.0</td>
<td>[46]</td>
</tr>
<tr>
<td>ArQ-Bios</td>
<td>Oval Medical Technologies (Waterbeach, U.K.)</td>
<td>Push-on-skin/2-step handling</td>
<td>Staked-needle prefilled syringe</td>
<td>Viewing window, click at injection start and end</td>
<td>Development</td>
<td>10.0</td>
<td>[53]</td>
</tr>
<tr>
<td>Gx Inbeneo</td>
<td>Gerresheimer (Düsseldorf, Germany)</td>
<td>Push-on-skin/2-step handling</td>
<td>Viewing window</td>
<td>Development</td>
<td>3.0</td>
<td></td>
<td>[56]</td>
</tr>
<tr>
<td>Maggie 5.0</td>
<td>SHL Technologies (Zug, Switzerland)</td>
<td>Push-on-skin/2-step handling</td>
<td>Rotating dial</td>
<td>Development</td>
<td>5.0</td>
<td></td>
<td>[57]</td>
</tr>
<tr>
<td>Ypsomate 5.5</td>
<td>Ypsomed (Burdorf, Switzerland)</td>
<td>Push-on-skin/2-step handling</td>
<td>Staked-needle prefilled syringe</td>
<td>Rotating dial, viewing window, continuous audible clicking</td>
<td>Development</td>
<td>5.5</td>
<td>[58]</td>
</tr>
</tbody>
</table>

First, increasing the subcutaneous injection volume and rate may intensify injection-site reactions, change the subcutaneous depot location, and increase pain [15,16,64,66]. Therefore, research on large-volume high-rate injections must examine injection tolerability as a necessary condition for regulatory approval and successful market uptake [67–69]. Second, manufacturers must ensure safe and effective drug self-administration, as autoinjectors help shift the point of care from the hospital to the home [29,70,71]. Regulators will scrutinize human factor validation to ensure users can perform self-injection at home [72,73]. In addition, patients must accept the administration of larger volumes, potentially resulting in longer injection time [36,74]. Third, the study of large-volume high-rate subcutaneous dosing with autoinjectors may lag behind the clinical evaluation of conventional subcutaneous injection methods [75,76]. Researchers may conduct large multicenter pivotal studies with safety and efficacy end points using conventional drug delivery methods and establish pharmacokinetic equivalence with emerging large-volume dosing options in subsequent bridging studies [77].

In conclusion, these three themes must be thoroughly understood to assess the feasibility of handheld autoinjectors for the subcutaneous administration of larger volumes. With that aim, this review article critically assesses the existing literature on large-volume subcutaneous drug delivery and structures their findings along injection tolerability, suitability for self-administration, and pharmacokinetic equivalence with existing dosing options. It then summarizes those questions prior work has answered, examines potential barriers to developing large-volume handheld autoinjectors, and concludes by highlighting promising areas for future research.

2. Review methods

The objective of this systematic literature review is to structure and synthesize previous work on subcutaneous administration of single large-volume doses (>1.0 mL) of a therapeutic agent. To identify relevant articles, the authors performed a multi-step review process. First, a Boolean search of the National Library of Medicine (pubmed.ncbi.nlm.nih.gov) was conducted using the keywords subcutaneous’, ‘injection’, ‘volume’, ‘pain’, and ‘tolerance’ (to account for different terms, such as tolerability or tolerance) in the title, abstract, or keywords. The authors then repeated the Boolean search on Google Scholar. Due to the large number of results and automatic sorting by article relevance, the review on Google Search was limited to the first 200 search results. These search results identified 602 articles, which the authors manually reviewed to determine whether the article focused on the study of large-volume subcutaneous injections. Of the studies considered relevant, the authors examined the references, engaged in repeated discussions, and collected relevant articles known to the authors before the systematic review to ensure that the study included all relevant articles. This multi-step process identified 31 articles that provided relevant insights into large-volume subcutaneous injections. The authors then organized the 31 articles based on their contributions to injection tolerability, suitability for self-administration, and pharmacokinetic equivalence with existing dosing options.

3. Review of current research

3.1. Overview of studied injection volume-rate ranges and themes

Figure 2 highlights the increasing interest in studying large-volume subcutaneous injections. While the first article on the area was published in 1996, 48% of the sample (15 articles) have appeared since 2020. Table 3 shows that previous work has explored various combinations of injection volumes and rates across different device technologies, including manual prefilled syringes and autoinjectors (1.0–2.0 mL; 0.1–0.9 mL/s), large-volume wearable injectors (5.0–10.0 mL; 0.02 mL/s), and manual large-volume syringes and syringe-type infusion pumps (15.0–60.0 mL; 0.01–0.1 mL/s). Figure 3 indicates that
previous studies have mainly focused on the large-volume/low-rate and the small-volume/high-rate ranges. Although several studies have addressed injection rates up to 0.9 mL/s, these have only studied injection volumes up to 2.0 mL. Conversely, injection rates were limited to around 0.1 mL/s for injection volumes significantly greater than 2.0 mL. Researchers have seldom examined large-volume/high-rate ranges, which would be most relevant to the new device category of large-volume handheld autoinjectors. These devices require injection rates of up to 0.5 –1.0 mL/s to achieve injection times of less than 15 s. In conclusion, only few findings directly apply to large-volume autoinjectors, and available data must be carefully evaluated before being extrapolated to the new device category.

Table 3 shows that prior work has covered all three themes critical to developing large-volume handheld autoinjectors. Although previous work has predominantly focused on advancing the injection tolerability theme (28 articles, 90% of the sample), 42% (13 articles) have contributed to the literature on suitability for self-administration. Thirty-two percent (10 articles) have advanced the pharmacokinetic equivalence theme. Five articles (16%) have covered all three themes, while 9 (29%) articles have addressed a combination of two of the three themes. The majority (17 articles, 55%) have provided insights into a single theme, leaving the others unaddressed.

3.2. Injection tolerability

3.2.1. Pain

Eighteen articles (58% of the reviewed articles) provide insights into the effects of injection volume and rate on injection-related pain. Table 3 shows that 16 studies evaluated pain using a 100 mm Visual Analog Scale (VAS). Fifteen of the 16 studies reported mild injection-related pain according to the VAS-based pain categories defined by Jensen and colleagues [100], while one study observed moderate-to-severe pain [95]. The authors attributed these higher pain levels to irritations caused by the citrate co-formulation, possibly masking the effects of the injection volume and rate on pain. Prior reviews concurred with these findings, highlighting that besides injection system design, dosing parameters, injection technique, and patient-related attributes, the drug formulation is a critical factor in determining pain level [64,101].

Table 4 provides an overview of the findings on the influence of injection rate and volume on pain. Nine studies examined the effect of increasing injection rates on pain. Results from eight studies showed no or no clinically relevant changes in pain. One study reported a significant decrease in pain with 3.5 mL injections administered in 10 min compared to 3.0 mL injected in 1 min [68]. However, the authors considered this difference clinically irrelevant due to the slight absolute increase in pain [68].

Table 4 shows that four studies found a significant positive relationship between injection volume and pain. For instance, a 3.5 mL injection in 1 min was more painful than a 1.2 mL injection over 5 s – even though the results do not show clinical significance [68]. Other studies also reported higher pain levels with larger volumes of 1.2 and 1.6 mL compared to lower volumes of 0.4 and 0.8 mL [84] or with volumes of 1.0 and 1.5 mL than for 0.2 and 0.5 mL [85]. Similarly, Zijlstra and colleagues [74] concluded that a single 2.25 mL injection caused significantly more pain

---

**Figure 2.** Evolution of previous research on large-volume subcutaneous drug delivery (N = 31), organized by three themes: injection tolerability, suitability for self-administration, and pharmacokinetic equivalence.

*Note: Some studies are represented multiple times in the respective year because they addressed more than one theme.*
<table>
<thead>
<tr>
<th>Reference</th>
<th>Study type</th>
<th>Device</th>
<th>Rate [mL/s]</th>
<th>Volume [mL]</th>
<th>Viscosity [cP]</th>
<th>Other</th>
<th>A. injection tolerability</th>
<th>B. Suitability for self-administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>[78] C</td>
<td>Infusion pump, manual push</td>
<td>0.007–0.028</td>
<td>25.0–50.0</td>
<td>-</td>
<td>Abdomen</td>
<td>-</td>
<td>&lt;10%, moderate site reaction</td>
<td>-</td>
</tr>
<tr>
<td>[15] C</td>
<td>Syringe pump</td>
<td>0.02–0.30</td>
<td>2.0–3.0</td>
<td>1–20</td>
<td>Abdomen</td>
<td>15–23</td>
<td>-</td>
<td>Mainly SC, some intradermal</td>
</tr>
<tr>
<td>[79] C</td>
<td>Manual syringe, auto-injector, patch injector, syringe pump</td>
<td>Up to 0.2</td>
<td>1.0–2.0</td>
<td>-</td>
<td>Thigh and abdomen</td>
<td>&lt;12</td>
<td>&lt;20% mild site reaction (except patch)</td>
<td>-</td>
</tr>
<tr>
<td>[80] P</td>
<td>Unspecified pump</td>
<td>0.04–0.16</td>
<td>10.0</td>
<td>-</td>
<td>Hyaluronidase</td>
<td>-</td>
<td>2.5% mild site reaction</td>
<td>-</td>
</tr>
<tr>
<td>[81] C</td>
<td>Infusion pump</td>
<td>0.008–0.033</td>
<td>-</td>
<td>-</td>
<td>Abdomen</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>[68] C</td>
<td>Syringe and infusion pump</td>
<td>0.006–0.24</td>
<td>1.2–3.5</td>
<td>S</td>
<td>Abdomen</td>
<td>3.5–20</td>
<td>30%, none serious</td>
<td>Some leakage</td>
</tr>
<tr>
<td>[53] C</td>
<td>Infusion pump</td>
<td>0.034–0.067</td>
<td>4.0–40.0</td>
<td>-</td>
<td>Hyaluronidase</td>
<td>&lt;15 (median)</td>
<td>100%, site reaction</td>
<td>-</td>
</tr>
<tr>
<td>[82] P</td>
<td>Syringe pump</td>
<td>0.016–0.10</td>
<td>1.0–10.0</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>&lt;10%, mild site reaction</td>
<td>Leakage &lt;1% of volume</td>
</tr>
<tr>
<td>[83] C</td>
<td>Manual syringe</td>
<td>-</td>
<td>2.0–3.0</td>
<td>-</td>
<td>Arm, thigh and abdomen</td>
<td>8% pain, not quantified</td>
<td>93% mild site reaction</td>
<td>-</td>
</tr>
<tr>
<td>[84] C</td>
<td>Syringe pump</td>
<td>0.15–0.45</td>
<td>0.15–1.60</td>
<td>-</td>
<td>Abdomen, thigh</td>
<td>≤30 (mean)</td>
<td>5%, mild site reaction</td>
<td>35% leakage, all &lt; 1% of volume</td>
</tr>
<tr>
<td>[66] C</td>
<td>Syringe pump</td>
<td>0.003–0.200</td>
<td>1.0–2.0</td>
<td>-</td>
<td>Abdomen</td>
<td>≤41 (mean)</td>
<td>95%, mild site reaction</td>
<td>-</td>
</tr>
<tr>
<td>[85] C</td>
<td>Manual syringe</td>
<td>-</td>
<td>0.2–1.5</td>
<td>-</td>
<td>Thigh</td>
<td>&lt;20 (mean)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>[86] C</td>
<td>Manual syringe</td>
<td>-</td>
<td>1.0–2.0</td>
<td>-</td>
<td>Arm, thigh and abdomen</td>
<td>&lt;7</td>
<td>&lt;10% mild site reaction</td>
<td>No leakage</td>
</tr>
<tr>
<td>[62] S</td>
<td>Patch injector</td>
<td>0.01</td>
<td>10.0</td>
<td>-</td>
<td>Abdomen, thigh</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

(Continued)
Table 3. (Continued).

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study type</th>
<th>Device</th>
<th>Rate [mL/s]</th>
<th>Volume [mL]</th>
<th>Viscosity [cP]</th>
<th>Other</th>
<th>Pain (VAS scores)</th>
<th>A. Injection tolerability</th>
<th>B. Suitability for self-administration</th>
<th>C. Pharmacokinetic equivalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>[87]</td>
<td>C</td>
<td>Manual syringe</td>
<td>-</td>
<td>4.5</td>
<td>0</td>
<td>Abdomen, temperature (8–37°C)</td>
<td>≤25 (median)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>[88]</td>
<td>C</td>
<td>Manual syringe</td>
<td>-</td>
<td>0.4–2.0</td>
<td>0</td>
<td>Abdomen, temperature (8–37°C)</td>
<td>-</td>
<td>1% site reaction, 20% AE (drug-related)</td>
<td>Strong preference for lower volume</td>
<td>-</td>
</tr>
<tr>
<td>[89]</td>
<td>C</td>
<td>Manual syringe</td>
<td>-</td>
<td>3.0</td>
<td>0</td>
<td>Abdomen, thigh</td>
<td>-</td>
<td>42% mild site reaction, no AE</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>[90]</td>
<td>S</td>
<td>Manual syringe</td>
<td>-</td>
<td>2.0</td>
<td>0</td>
<td>Needle cannula length &amp; type</td>
<td>-</td>
<td>-</td>
<td>Confirmed shorter cannula preferred</td>
<td>-</td>
</tr>
<tr>
<td>[91]</td>
<td>C</td>
<td>Manual syringe</td>
<td>0.133–0.40</td>
<td>2.0</td>
<td>0</td>
<td>Abdomen, thigh</td>
<td>9.5–27 (mean)</td>
<td>36% mild site reaction, no AE</td>
<td>Confirmed</td>
<td>-</td>
</tr>
<tr>
<td>[92]</td>
<td>P</td>
<td>Auto-injector</td>
<td>0.0625–0.83</td>
<td>2.0</td>
<td>0</td>
<td>Needle cannula length &amp; type</td>
<td>-</td>
<td>Leakage &lt;1% of volume SC</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>[36]</td>
<td>S</td>
<td>Autoinjector</td>
<td>0.07</td>
<td>2.0</td>
<td>0</td>
<td>Abdomen</td>
<td>-</td>
<td>-</td>
<td>Confirmed for injection times up to 30s</td>
<td>-</td>
</tr>
<tr>
<td>[93]</td>
<td>C</td>
<td>Infusion pump, manual push</td>
<td>0.025–0.11</td>
<td>3.0–20.0</td>
<td>0</td>
<td>Abdomen</td>
<td>-</td>
<td>31% mild site reaction</td>
<td>Manual push preferred Confirmed</td>
<td>-</td>
</tr>
<tr>
<td>[94]</td>
<td>C</td>
<td>Infusion pump, manual push</td>
<td>-</td>
<td>&lt;60</td>
<td>0</td>
<td>Abdomen</td>
<td>-</td>
<td>16–21% AEs, primarily local</td>
<td>Manual push preferred Confirmed</td>
<td>-</td>
</tr>
<tr>
<td>[95]</td>
<td>P, C</td>
<td>Auto-injector, manual syringe</td>
<td>0.083–0.5</td>
<td>1.0–2.0</td>
<td>0</td>
<td>Injection depth, hyaluronidase</td>
<td>30–100, drug-related</td>
<td>Leakage &lt;1% of volume</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>[31]</td>
<td>C</td>
<td>Manual syringe</td>
<td>-</td>
<td>1.0–2.0</td>
<td>0</td>
<td>Abdomen</td>
<td>-</td>
<td>&lt;6% mild site reaction, up to 80% AEs, drug-related</td>
<td>Confirmed</td>
<td>-</td>
</tr>
<tr>
<td>[96]</td>
<td>C</td>
<td>Manual syringe</td>
<td>0.1–0.3</td>
<td>4.5</td>
<td>0</td>
<td>Abdomen</td>
<td>24–26 (mean)</td>
<td>-</td>
<td>Preference independent of rate</td>
<td>-</td>
</tr>
</tbody>
</table>

(Continued)
### Table 3. (Continued)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study type</th>
<th>Device</th>
<th>Rate [mL/s]</th>
<th>Volume [mL]</th>
<th>Viscosity [cP]</th>
<th>Other</th>
<th>Pain (VAS scores)</th>
<th>AE and injection-site reactions</th>
<th>Leakage</th>
<th>Fluid depot location</th>
<th>Usability</th>
<th>Adherence, preference</th>
<th>C. Pharmacokinetic equivalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>[97]</td>
<td>C</td>
<td>Patch injector, syringe pump</td>
<td>0.017</td>
<td>3.0</td>
<td>-</td>
<td>Abdomen</td>
<td>2–22 (mean)</td>
<td>No AEs reported</td>
<td>No or minimal leakage</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>[98]</td>
<td>C</td>
<td>Infusion pump</td>
<td>0.006</td>
<td>15.0</td>
<td>-</td>
<td>Abdomen, thigh</td>
<td>-</td>
<td>28% AEs, mainly site reactions</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>[61]</td>
<td>C</td>
<td>Patch injector</td>
<td>0.015</td>
<td>5.0</td>
<td>8</td>
<td>Abdomen, thigh</td>
<td>9.1 (mean)</td>
<td>75% mild site reactions, no injection-related AEs</td>
<td>-</td>
<td>99% SC</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>[99]</td>
<td>C</td>
<td>Syringe pump</td>
<td>0.02</td>
<td>5.0–10.0</td>
<td>1–20</td>
<td>Abdomen, thigh</td>
<td>&lt;27 (mean)</td>
<td>92% mild site reactions</td>
<td>Leakage &lt;1% of volume</td>
<td>42% SC, 56% SC and intradermal</td>
<td>-</td>
<td>Pain and site reaction acceptability &gt; 85%</td>
<td>-</td>
</tr>
<tr>
<td>[74]</td>
<td>C</td>
<td>Syringe pump</td>
<td>0.00–0.80</td>
<td>0.00–2.25</td>
<td>-</td>
<td>Abdomen, thigh</td>
<td>≤15 (mean)</td>
<td>100% mild site reactions</td>
<td>Leakage &lt;1% of volume</td>
<td>-</td>
<td>Pain acceptance &gt; 94%</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Note: **Abbreviations.** AE: Adverse events, P: Pre-clinical animal study, C: Clinical in-human study, S: Simulated use study, SC: Subcutaneous.
than injections of 0.1, 0.4, and 0.8 mL. Conversely, five articles found no significant or clinically relevant effects of injection volume on pain. However, the literature review does not provide conclusive evidence on the design space for large-volume autoinjectors, thus inviting further investigations to validate these aspects for injection volumes between 2.0 and 10.0 mL administered within less than 1 min.

Two studies analyzed the impact of fluid viscosity on perceived pain, with one study finding a statistically significant negative relationship [15] and the other no significant effect [61]. These conflicting results may be due to differences in experimental design, such as the device type used (syringe pump versus wearable injector), the injection volume (2.0–3.0 mL versus 5.0 mL), and the injection rate (0.02–0.30 mL/s versus 0.02 mL/s). Two studies found higher pain with injections into the thigh compared to the abdomen [74,84].

3.2.2. Adverse events and injection-site reactions
Twenty-two studies (71.0%) examined the incidence of adverse events (AEs) and injection-site reactions. Table 4 provides a summary of the effect of injection volume and rate on AEs.

No study reported any injection-related AEs except for injection-site reactions. In two cases, drug-related AEs were reported [31,88]. The occurrence of injection-site reactions varied greatly, ranging from 2.5% up to 100.0% of injections, highlighting how drug product-specific attributes may mask the effects of injection parameters [53,74,81,95]. Reactions typically observed at the injection site were redness, itching, and swelling; in some cases, hematomas or bleeding occurred. Bruising, which has been reported in other work on the tolerability of subcutaneous drug delivery using autoinjectors [102–104], was mentioned in only few of the studies [31,61,84,86,95]. While most injection-site reactions were mild, one study reported moderate injection-site reactions [78] and another study reported severe injection-site reactions [79]. The authors of the latter study attributed the severe injection-site reactions to the use of a novel injection patch rather than injection volume or rate. This study therefore highlights that the injection device technology can have a significant impact on AEs.

Out of the 14 studies that evaluated the relationship between injection volume and injection-site reactions or injection-related AEs, four studies found a positive correlation between the two variables (two on the severity of AEs and two on the frequency of AEs), while 10 studies did not observe any correlation (Table 4).

Eleven studies examined the influence of injection rate on the frequency of injection-site reactions and injection-related AEs. One study found a positive correlation between the two variables [66], while 10 observed no effects. None of these studies performed a statistical analysis determine significance.

3.2.3. Injection-site leakage
Ten articles (32.2%) investigated the occurrence of injection-site leakage (Table 3). The review showed that when injection-site leakage did occur, it was only in small amounts, and the injection parameters had little to no impact on its occurrence. Therefore, this review suggests that injection-site leakage can be considered negligible from both a practical and clinical perspective. Out of the 10 studies, eight studies observed no or minimal leakage (less than 1.0% of the injection volume), while one study reported ‘some’ leakage [68]. Another study observed ‘limited’ leakage of around 2.0% of the injection volume [66]. Zijlstra and colleagues [74] found that leakage increased with increasing volume but remained below 1.0% of the injected volume. They also confirmed that the amount of leakage met the acceptable accuracy requirements in 99.6% of the cases as per the relevant standard. Similarly, Doughty and colleagues [82] observed increased leakage for high-viscosity solutions, but it was still below 1.0% of the injection volume. Another study showed that injection-site leakage decreased with increasing injection depth but remained below 1.0% across scenarios studied [95]. The remaining studies found no significant effects of injection volume, rate, or fluid viscosity on leakage.

3.3. Suitability for self-administration
Of the 31 articles reviewed, four (12.9%) focused on the safe and effective use of large-volume injection devices, and 10 (32.3%) studied user preferences, such as treatment acceptance and satisfaction. A single article studied both usability and user preference (Table 3). The review found broad agreement in support of the safe and effective administration of large-volume doses [78,81]. However, previous research has been inconclusive on how injection parameters, such as volume and rate, impact user preference.

Studies have confirmed the safe and effective use of 2.0 mL prefilled syringes [31,90] and handheld autoinjectors [36]. A phase 3 clinical trial on patient ease of use and satisfaction concluded that 88% of patients completed all required user steps and 90% reported being very satisfied or satisfied with large-volume self-injection [31]. Pager and colleagues [90] found that a new 8.0 mm needle improved user experience for 2.0 mL injections with high-viscosity fluids compared to existing 12.7 mm needle syringes. Although large-volume doses translate into longer injection duration, Schneider and colleagues [36] showed that participants in a simulated use study successfully completed injections up to 30 s with an autoinjector, regardless of disease state, age, or visual and dexterity limitations. Researchers consistently reported high patient satisfaction with high-volume injections across device categories, including large-volume wearable injectors. For instance, Lange and colleagues [62] found high user acceptance for a large-volume wearable injector. While these insights have important implications for future device design and development, the simulated study design limits their findings to user-related aspects, thus remaining silent on others, such as pain or injection-site leakage. Woodley, Morel et al. [99] fill these gaps with their in-human study and found that patients favorably perceived self-injection of 5.0 mL with a wearable large-volume injector and would use the device if prescribed.

This review uncovers conflicting results regarding user preferences for different large-volume dosing options. Kokolakis, Kreis et al. [86] found patients prefer a single large-volume
injection (2.0 mL) over two separate small-volume injections (1.0 mL each), while Müller-Ladner and colleagues [88] found a strong user preference for smaller single-dose volumes. Preferences also varied depending on the injection rate. As such, Shapiro [93,94] found patient preferences for high-rate subcutaneous injection over slow infusion-pump-enabled administration. In contrast, Tangen et al. [96] concluded that patient preferences for subcutaneous injection of 4.5 mL lidocaine were robust to changes in injection rate (0.1–0.3 mL/s) and duration (15 s – 45 s).

3.4. Pharmacokinetic equivalence with existing dosing options

Table 5 summarizes the results of the 10 articles that studied pharmacokinetic (PK) equivalence of different drug delivery methods. The review found that changing from multiple low-volume to a single large-volume injection does not affect PK profiles and bioavailability [31,66,79,86]. For instance, the serum exposure of 300 mg secukinumab from a single 2.0 mL dose was similar to two sequential 1.0 mL injections [31,79]. Another study found no differences in the PK profile of tralokinumab when comparing different injection rates of a single 2.0 mL injection with two sequentially administered 1.0 mL injections [66]. Comparing two 1.0 mL injections with a single 2.0 mL subcutaneous injection, a clinical study on tildrakizumab found supportive evidence [86].

Changing the injection rates while keeping the injection volume constant did not change the PK profiles [66,79,91]. For example, Portron et al. [91] found no statistically significant differences in the PK profiles of gantenerumab patient groups with an injection time of 5 and 15 s. Similarly, varying the time

Figure 3. Overview of injection volume-rate ranges addressed by previous work and volume-rate ranges applicable to different device categories.

Table 4. A summary of review results for injection tolerance themes, including injection-related pain, injection-site reactions, and adverse events.

<table>
<thead>
<tr>
<th>Injection parameters</th>
<th>Positive</th>
<th>None</th>
<th>Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. Effects† of injection parameters on pain (VAS score)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injection rate</td>
<td>n = 1 (11.1%)</td>
<td>[68]</td>
<td>[15,53,66,74,84,91,95,96]</td>
</tr>
<tr>
<td>(N = 9)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injection volume</td>
<td>n = 4 (44.4%)</td>
<td>[68,74,84,85]</td>
<td>[15,53,79,86,99]</td>
</tr>
<tr>
<td>(N = 9)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluid viscosity</td>
<td>n = 0 (0.0%)</td>
<td>-</td>
<td>[99]</td>
</tr>
<tr>
<td>(N = 2)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| **B. Effects‡ of injection parameters on occurrence of injection-site reactions and AEs** |           |      |          |
| Injection rate       | n = 1 (9.1%) | [66] | [53,68,74,79,81,82,84,91,93,95] | n = 0 (0.0%) | - |
| (N = 11)             |           |      |          |           |      |        |
| Injection volume     | n = 4 (28.6%) | [53,66,88,99] | [31,68,74,79,82–84,86,93,95] | n = 0 (0.0%) | - |
| (N = 14)             |           |      |          |           |      |        |

Note: †The authors categorized effects as Positive, Negative, or None based on statistical significance and clinical relevance.
‡Qualitative observations were also assigned to Positive or Negative, without further statistical analysis.
required to inject 2.0 mL secukinumab between 5 min and 10 s did not affect the PK profile [79].

Studies examining large-volume injections of monoclonal antibodies and immunoglobulins concluded that increasing the injection volume and rate did not affect serum concentrations [53,78,81,93,94]. Larger injection volumes (<50.0 mL) and rates (<0.028 mL/s) did not impact safety and tolerability of immunoglobulins, simplified overall administration, and reduced the number of injection sites and injection duration [78]. Cowan and colleagues [81] also concluded that increasing injection rates up to 0.033 mL/s did not change immunoglobulin serum levels. These findings were consistent for patient cohorts with manual push-type infusion and pump-assisted delivery [78,93,94]. Subcutaneous injection of crenezumab doses up to 40.0 mL (7200 mg) neither affected pharmacokinetics nor bioavailability parameters [53]. Adding recombinant hyaluronidase improved PK profiles compared with intravenous infusion and subcutaneous bioavailability [53]. The latter results have important implications for the development of large-volume injectors and show that adapting a formulation to meet the requirements of large-volume high-rate injections may affect PK equivalence.

4. Future research directions

4.1. Toward an agenda for future research

This review analyzes 31 articles on large-volume subcutaneous delivery and organizes their findings into three themes critical to the development and approval of large-volume autoinjectors: injection tolerance, suitability for self-administration, and pharmacokinetic equivalence. These themes are not only helpful in organizing the existing literature but also provide the basis for categorizing future research, as outlined in Table 6. First, the review results call for future studies within the three themes that address questions related to high-rate injections with high-volume autoinjectors. Second, they highlight the need for integrative work that spans the three themes. Advancing topics at the intersection of these themes will promote comprehensive views of the feasibility of large-volume autoinjectors, and help address critical trade-offs in their design and development.

4.2. Future research within themes

The review analyzed prior research on large-volume subcutaneous injections across therapeutic contexts and device categories, such as manual syringes [31], syringe pumps [61,66,84], wearable large-volume injectors [61,97], and handheld autoinjectors [36,95]. While these studies advance understanding of large-volume subcutaneous injections in general, they do not address certain issues specific to high-rate and large-volume injections with handheld devices (Figure 3). Therefore, this review suggests avenues for future work on large-volume autoinjectors within the three themes (Table 6).

This review advances the key insight that although higher injection volume and rate may increase pain, the impact was low on the pain scale (Table 4), and drug formulation may mask these effects [95]. These findings inform future work on handheld autoinjectors for high-volume dosing. Effective subcutaneous dosing with handheld autoinjectors will likely hinge on new formulations that allow rapid absorption of highly concentrated biologics in subcutaneous tissue [65,105]. For instance, the co-formulation of the dispersion enhancer hyaluronidase has effectively improved subcutaneous delivery [95]. Still, new formulations may also affect pain perceptions. Pain is particularly significant in the case of large-volume autoinjectors, as users may remove the device prematurely from the injection site during prolonged injection times if it is too painful [36]. Future work should therefore study the impact of such formulation advances on pain-related clinical outcomes.

This review invites future work to study the effects of high-volume autoinjectors on injection-related pain, adverse events, and injection-site leakage (Table 6). Bruin and colleagues [79] have reported a new injection patch to cause severe injection-site reactions. Therefore, future research must ensure that the design of new high-volume autoinjectors does not cause such AEs. Various technical attributes of handheld devices, such as the user forces required to trigger the device or the type or design of the needle shield pressed against the injection site, should be considered in optimizing device design to prevent excessive tissue pressure, back-flow and leakage of injected solution, and tissue damage. In fact, previous work has shown that tissue resistance can cause problems with autoinjectors for subcutaneous injection [106]. These studies will provide a more complete understanding of the challenges specific to high-volume injectors.

This review presents strong evidence of the feasibility of self-administering single large-volume doses. Researchers have demonstrated safe and effective use for handheld autoinjectors up to 2.25 mL [16,36], wearable large-volume injectors [62,97,99], and large-volume manual syringe and infusion pumps [93,94]. In particular, studies show that increasing injection volume and time was feasible for handheld autoinjectors [36]. However, the review shows conflicting views on user preferences for different dosing options [86,88,93,94,96]. Future work should therefore examine how user preferences for large-volume autoinjector-based dosing options change with changes in dosing regimens. Previous studies have

Table 5. A summary of review results for pharmacokinetic equivalence theme.

<table>
<thead>
<tr>
<th>Studied injection parameters</th>
<th>Injection rates [mL/s]*</th>
<th>Volume range [mL]*</th>
<th>Effect on PK profiles</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple low-volume injections versus a single large-volume injection</td>
<td>0.003–0.200</td>
<td>1.0–2.0</td>
<td>None</td>
<td>[31,66,79,86]</td>
</tr>
<tr>
<td>Change in injection rate</td>
<td>0.003–0.400</td>
<td>1.0–2.0</td>
<td>None</td>
<td>[66,79,91]</td>
</tr>
<tr>
<td>Change in injection volume and rate</td>
<td>0.007–0.11</td>
<td>3.0–60.0</td>
<td>None</td>
<td>[53,78,81,93,94]</td>
</tr>
</tbody>
</table>

NOTE: * Overall extreme values of the injection parameters studied across the empirical work included in the review.

Abbreviations: PK: pharmacokinetics.
Table 6. Proposed future research topics classified by theme.

<table>
<thead>
<tr>
<th>Future research topic</th>
<th>A. Injection tolerability</th>
<th>B. Suitability for self-administration</th>
<th>C. Pharmacokinetic equivalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Injection tolerability</td>
<td>• Effects of device technical attributes (e.g. needle guard geometry) on injection tolerability</td>
<td>• What injection duration keeps pain low while ensuring safe and effective device use (i.e. no premature removal due to pain)</td>
<td>Injection tolerability/pain-related end points in pharmacokinetic bridging studies</td>
</tr>
<tr>
<td></td>
<td>• User-related forces and their relationship with pain and injection-site leakage (e.g. force required to trigger injection)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Relative importance of injection volume and rate versus other drug-specific parameters (e.g. formulation) for injection tolerance</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Pain related with large-volume autoinjectors versus other device categories (e.g. syringe pumps and wearable large-volume devices)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B. Suitability for self-administration</td>
<td></td>
<td>• Optimizing user experience and interface for prolonged injection duration (e.g. continuous injection feedback)</td>
<td>Virtual at-home clinical trials to include usability-related end points and self-assessment on patient preference</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• User preferences for different autoinjector-based dosing options (e.g. injection duration versus frequency)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• User preferences across high-volume device alternatives (e.g. manual syringes vs handheld autoinjectors vs syringe pumps vs wearable large-volume injectors)</td>
<td></td>
</tr>
<tr>
<td>C. Pharmacokinetic equivalence</td>
<td></td>
<td></td>
<td>Impact of formulation advances that enable rapid injection of high-concentration biologics on pharmacokinetic profiles Validation of robustness of pharmacokinetic profile against changes in injection frequency Innovative approaches to molecule-independent pharmacokinetic bridging to simplify access to large-volume autoinjectors</td>
</tr>
</tbody>
</table>

shown that injection duration and frequency play a significant role in treatment choices and adherence [1,51,107–109]. Moreover, the review calls for future work on user preferences across device categories, such as manual syringes, handheld autoinjectors, wearable large-volume injectors, and syringe pumps. As the variety of devices continues to increase, research must provide health-care professionals and patients with the necessary evidence to make treatment decisions for optimal adherence and therapy outcomes.

The review found the pharmacokinetic profiles to be stable in response to changes in injection parameters (Table 5). These findings are in line with the slow absorption rate of therapeutic proteins from the subcutaneous extracellular matrix [8]. However, previous studies have mainly focused on switching from multiple small-volume injections to a single large-volume dose without adjusting the time intervals between injections [31,66,79]. Future research should examine the effects of reducing injection frequency using large-volume autoinjectors on pharmacokinetic equivalence. Such a shift in dosing could potentially lead to improved treatment adherence and patient preference [51,107].

This review also highlights the potential for future work to evaluate novel approaches to assess the pharmacokinetic equivalence of high-volume autoinjectors compared to low-dose injections given more frequently. Currently, new subcutaneous dosing options are established through dedicated drug-by-drug bridging studies [76]. However, future work could consider molecule-independent approaches to clinical bridging [110] to facilitate access to and accelerate the time-to-market of new large-volume handheld autoinjectors.

4.3. Future research across themes

This review highlights that 55% of the articles advanced understanding of a single theme while not addressing others (Table 3). Although 29% of the articles combined two themes, only a limited number (16%) provided an integrated perspective on all three themes. Limited resources and complexities in research design limit the number of themes one can address in a single study. However, researchers need to acknowledge the risk of isolation of each of the three themes. Studies that advance insights within a single theme are problematic because they can lead to lop-sided empirical work that selectively emphasizes some aspects and ignores others. Blind spots at the intersection of themes can result in incomplete knowledge, which is an impediment to effective decision-making during the development of large-volume autoinjectors.

Therefore, this review underscores the importance of considering all three themes and developing an encompassing view of large-volume high-rate injections with handheld devices. Consider, for example, an innovative clinical trial
design to bridge the current small-volume to new large-volume autoinjectors. Patients would administer multiple small-volume doses followed by a single large-volume autoinjector dose. In addition to reporting pharmacokinetics-related end points, the study may also examine pain perceptions, monitor use errors, and assess perceived ease of use and overall treatment satisfaction. Such a study could provide insights into injection tolerability, device usability, and pharmacokinetic equivalence, enabling broad adoption of handheld autoinjectors in clinical practice.

Another example of a research question that arises only at the intersection of the three themes is addressing the inherent trade-offs between injection tolerance, suitability for self-administration, and injection duration (Table 6). While lower-rate injections may result in reduced pain [95], longer injection durations may increase the risk of use errors [36]. Addressing this challenge through innovative research designs could lead to better informed specification of the injection time of large-volume handheld autoinjectors. Thus, the illustrative example re-emphasizes the importance of intertwining themes and calls for innovative research designs that provide integrated insights spanning injection tolerance, suitability for self-administration, and pharmacokinetic equivalence.

5. Conclusion

This review critically evaluates the existing literature on large-volume subcutaneous injections to assess the feasibility of large-volume handheld autoinjectors. The study structures the findings of previous work along three themes critical to large-volume autoinjector development. Despite the lack of prior work specifically studying autoinjectors exceeding 2.0 mL volume capacity, the review demonstrates that the insights provided by existing literature are relevant to and support using handheld autoinjectors for large-volume single-dose delivery. The review also identifies two areas for future research. First, it encourages scholars to address the specific challenges related to injection tolerability, suitability for self-administration, and pharmacokinetic equivalence in the context of handheld autoinjectors. Second, the review suggests integrating the three themes to develop a comprehensive view of large-volume high-rate injections and avoid lopsided empirical work that selectively emphasizes some aspects while neglecting others.

6. Expert opinion

The study of large-volume subcutaneous drug delivery has developed into a vibrant field of research, where scholars have made significant headway in exploring the upper limits of subcutaneous injection. While researchers have yet to convince the industry, health-care providers, patients, and regulatory authorities of the feasibility of large-volume handheld autoinjectors for volumes between 2.0 and 5.0 mL or even beyond, the review provides a valuable basis for developing these new dosing options. With the increasing demand for safe and effective self-administration options, large-volume autoinjectors could soon gain a foothold in the market.

Autoinjectors have effectively emerged as a viable option for safe and effective subcutaneous self-injection of up to 2.0 mL (Table 1). Handheld devices for single doses exceeding 2.0 mL would be the next step in this incremental development. These devices under development (see Table 2) leverage the well-accepted and proven push-on-skin handling principle [29,111] and may allow more seamless health-care provider and patient onboarding with lower training requirements. This is in contrast to large-volume wearable devices, which deviate more fundamentally from the standard handling principles of handheld devices [51,59,62,99].

Furthermore, large-volume autoinjectors leverage the potential of established technologies, manufacturing processes, and regulatory pathways, while other emerging device categories, such as capsules for the oral delivery of biologics [112] or needle-free injectors [113], pose additional challenges and require different kinds of expertise, development processes, and innovation routines. These advantages enable pharmaceutical companies to reinforce existing capabilities, mitigate risks in device development, and accelerate time-to-market. For example, some large-volume autoinjector device platforms are largely compatible with existing infrastructures and manufacturing processes, such as fill-finish, final assembly, and packaging (cf. Table 2).

Finally, large-volume handheld autoinjectors reduce injection duration (Figure 3), which has been shown to increase treatment preference and contribute to the widespread market acceptance of subcutaneous drug delivery [1,51,93]. By allowing for faster injection of large single-volume doses, large-volume autoinjectors may further boost the acceptance of subcutaneous injections.

While large-volume autoinjectors offer significant potential benefits, these devices also face barriers to adoption. Pharmaceutical manufacturers must establish new primary packaging suitable for high-volume drug delivery and address questions around high-concentration drug formulation, process development, analytical methods, and drug stability [114,115]. For investigational new drugs where time-to-market is critical, pharmaceutical manufacturers are more likely to adopt well-characterized syringes or cartridges for low-volume dosing systems and turn toward innovative large-volume dosing options only later in the life cycle management process.

In conclusion, large-volume handheld autoinjectors have the potential to offer new dosing regimens for drugs already injected subcutaneously and to expand subcutaneous injections to new fields, such as cancer care [1,52]. Hence, these devices may become instrumental in broadening access to innovative medicine as they help shift the point of care from the hospital to the home. In oncology, for example, efforts are underway to establish more flexible care concepts where nurses can perform at-home injections [3,116] and patients self-report symptoms during therapy [117,118]. The high-rate delivery of biologics with large-volume autoinjectors may further improve patient satisfaction, reduce healthcare resource utilization, and increase advantageous effects on total health care and societal costs of subcutaneous drug administration. However, patient preferences for devices and dosing regimens are
complex and subject to change [51,107,108]. Thus, we anticipate multiple dosing options to co-exist in the future, providing more flexibility to personalize treatment decisions to patients’ diverse needs. The potential benefits to patients and health-care providers make handheld autoinjectors for the subcutaneous delivery of large-volumes a field worth exploring.

Acknowledgments

The authors are grateful to Mathias Romacker and Ian Thompson for their critical review of and insightful contributions to the competitive and market analysis of high-volume subcutaneous drug delivery.

Funding

This paper has been sponsored by Ypsomed AG

Declaration of interest

The authors are employed by Ypsomed AG. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

ORCID

Jakob Lange  http://orcid.org/0000-0002-3018-8265

References

Papers of special note have been highlighted as: (*) of interest (**) of considerable interest


• Presents subcutaneous injection as the preferred treatment option of breast cancer patients.


European double-blind, using Regeneron. Novartis.


Perspectives drusatfda_docs/label/2017/761032lbl.pdf

Full injection, for subcutaneous use. 2023. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761224s000lbl.pdf

Takeda. Full Prescribing Information: TAKHZYRO (lanadelumab-flyo) injection, for subcutaneous use. Lexington MA: Takeda; 2022.

Aktiv. ARAI is the next generation rescue auto-injector for life threatening conditions 2023 [cited 2023 16 feb]. Available from: https://aktivpharmagroup.com/rescue-auto-injector

Signurgeirsson B, Browning J, Tyring S, et al. Secukinumab demonstrates efficacy, safety, and tolerability upon administration by 2 ml autoinjector in adult patients with plaque psoriasis: 52-week results from MATURE, a randomized, placebo-controlled trial. Dermatologic Therapy. 2022;25(3):15285. DOI: 10.1111/dth.15285


• Presents the results of a 40ml high-volume injection of a monoclonal antibody and the effects of a dispersion enhancer on subcutaneous drug delivery.


**Review summarizing the challenges and future research directions of high-volume subcutaneous delivery.**


**Clinical study on the relationship between subcutaneous dosing options and injection tolerability and pharmacokinetics.**


**Clinical study on the high-rate injection of single large-volume doses exceeding 2ml.**
