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HOW LONG CAN YOU HOLD THE DEVICE AGAINST THE SKIN? INSIGHTS FROM AN EMPIRICAL STUDY USING HAND-HELD AUTOINJECTORS

In this article, Andreas Schneider, PhD, Innovation and Business Development Director at Ypsomed, summarises recent empirical work investigating the ability of users of hand-held devices to complete longer injection times effectively. The study provides insights into the effects of injection duration on the force exerted by the user to hold the device against the injection site. It also highlights whether and how the characteristics of patient groups affect their ability to withstand longer injection duration, and considers the upper feasible limit of injection duration.

QUESTIONING THE FEASIBLE UPPER LIMIT OF INJECTION DURATION FOR AUTOINJECTORS

The drug delivery industry has long debated over the subcutaneous delivery of single high-dose volumes with handheld prefilled autoinjectors. Technological advances, combined with a better understanding of the pharmacokinetics and tolerability of single large-volume doses, have led to a reconsideration of the subcutaneous administration of 1 mL within 10 seconds as the upper feasible limit for autoinjectors. In fact, the approval of two recent landmark products provides evidence that regulatory agencies support longer, high-volume injections to reduce injection frequency further, minimise patients' day-to-day lifestyle disruptions and improve therapy outcomes.

First, Teva Pharmaceutical Industries has received US FDA approval for a high-volume prefilled autoinjector device for its migraine-treatment drug AJOVY® (fremanezumab-vfrm). The two-step autoinjector, based on the YpsoMate 2.25 mL platform, enables the safe and effective administration of a single dose of 1.5 mL (225 mg). Figure 1 illustrates the single-use prefilled high-volume AJOVY® autoinjector.

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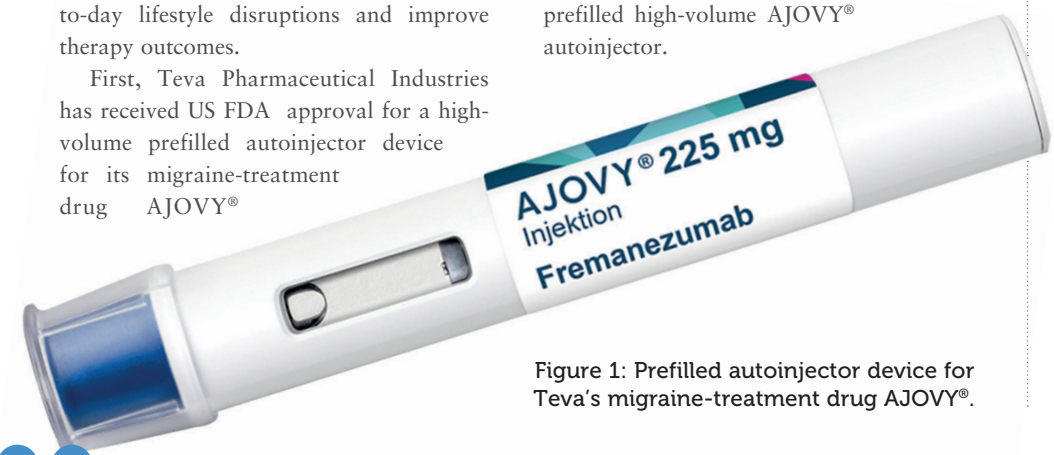

Figure 1: Prefilled autoinjector device for Teva's migraine-treatment drug AJOVY®.

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Figure 2: The market-proven company: 2-step YpsoMate 2.25 autoinjector platform.

Second, the FDA also approved Regeneron and Sanofi's Dupixent® (dupilumab) prefilled autoinjector for all indications in patients aged 12 years and older. The device allows patients to self inject a single high-volume dose of 2.0 mL (300 mg).

However, studies have shown that large single doses translate into longer injection times to avoid higher perceived pain, subcutaneous pressure and injection site leakage. Interestingly, there is limited evidence of the feasibility of longer injections when using hand-held autoinjectors. There is much at stake. The safe and effective use of the device is a necessary condition for effective product approval and commercial uptake. Therefore, it is of utmost importance to understand better how long patients are able to hold autoinjectors against the skin to successfully complete a self-injection. Also, more insights are needed on how different user groups, such as elderly and dexterity-impaired individuals, cope with the longer injection duration.

A SENSOR-AUGMENTED APPROACH

The simulated-use study[1], based on single-site visits, included 32 adolescent, adult and elderly patients across chronic disease states, non-professional caregivers and healthcare professionals. All patients suffered from at least one chronic disease state that offers autoinjector-based treatment options. The participants performed three simulated injections at increasing pre-set injection times that ranged from approximately seven to 30 seconds.

The prefilled single-use YpsoMate 2.25 mL autoinjector was included in the study (Figure 2). Its push-on-skin release and audible and visual feedback provides high patient confidence and convenience during drug self-administration. Users first push the single-use autoinjector on skin to initiate the injection and then sustain a minimum force to hold the device against the skin to complete the injection.

The participants performed the injections in a custom-built foam cushion with embedded force sensors. While attached to the abdomen of the participants, the sensors continuously tracked the user's force-time curve for each simulated injection. Figure 3 shows the experimental set-up used for data collection.

Figure 4 illustrates a typical user's force-time curve obtained for each simulated injection. Data included the time at which the users applied the minimum, mean and maximum force during the injection. The data points were then used to quantitatively assess the impact of the injection duration on the user's ability to effectively perform injections.

RE-THINKING THE CURRENT UPPER FEASIBLE LIMIT OF INJECTION DURATION

The simulated-use study confirms that participants are able to use handheld autoinjectors to administer single high-volume injections, which last longer than 10 seconds, to deliver the actual medication. Increasing the injection duration to 30 seconds did not lead to any usage errors, usage difficulties or further deviations from the usage instructions. Usage errors occurred, if at all, due to lack of training and participants' familiarisation with the instructions for use. Patient characteristics, such as dexterity impairments, gender,

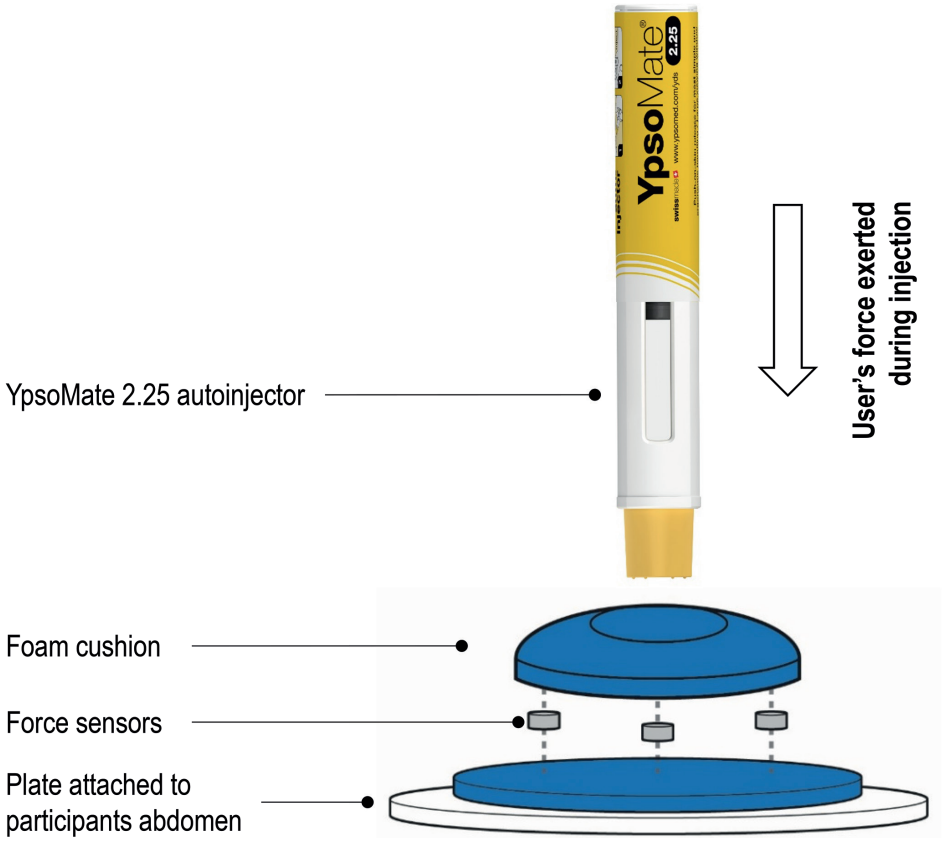

Figure 3: Experimental set-up to capture the user's force-time curve.

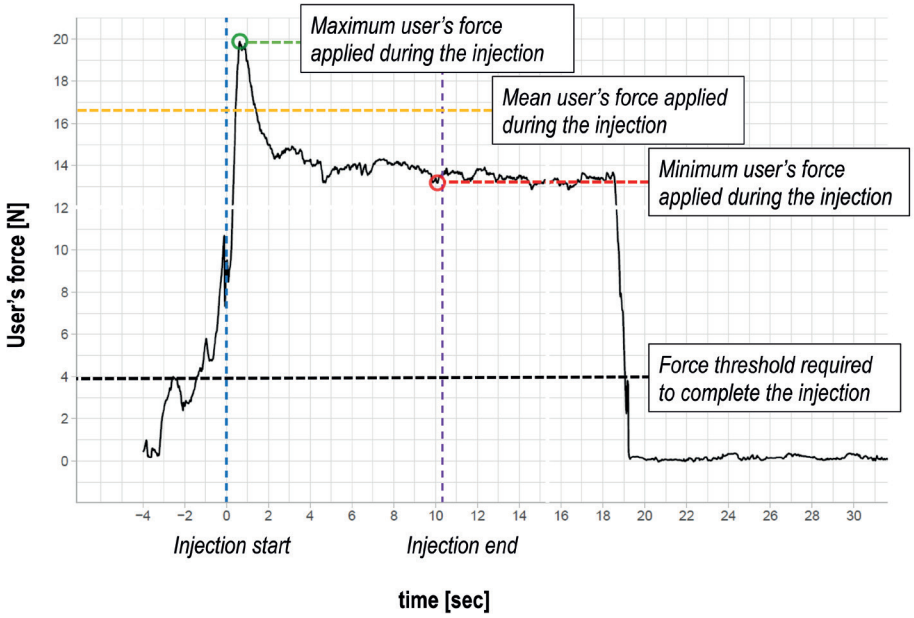

Figure 4: Illustration of a typical user's force-time curve.

injection experience and age-related conditions did not negatively impact the user's ability to effectively complete longer injection durations.

Contrary to our expectations, the study revealed that elderly patients actually exerted a higher mean force than adolescent patients when holding the device against the skin. Although prior studies have highlighted how grip strength decreases with age, the results did not confirm any age-related effects for the overall user population. In fact, older patients' awareness of impairments that may limit the effective performance of longer injections can lead to overcompensation and thus result in higher downward pressure on the autoinjector during the injection.

INJECTION DURATION OF 50 SECONDS WITH HAND-HELD AUTOINJECTORS?

These insights advance our understanding of how injection duration influences the user's ability to hold the device against the skin. First, the study revealed a significant, yet small, negative effect of the injection duration on the minimum and mean user's force exerted during the injection. Extending the injection duration by one additional second reduced the minimum and mean user's force exerted to hold the device against skin by 1.3% and 1.1%, respectively.

The force reduction for the one-second increase in injection duration has important implications for the design and development of new autoinjector devices. The results suggest, for example, that an average user may be able to complete injections effectively with a target injection duration of 50 seconds, using a handheld autoinjector that requires approximately 15 N to trigger the injection and a minimum force of 4 N to hold the device against the skin during the injection.

Interestingly, the market is already moving in this direction. For example, the full prescribing information of the AJOVY® prefilled autoinjector instructs the user to keep holding the device down against the skin for about 30 seconds. Although theoretically feasible, the suitability of even longer injection times must be carefully balanced with user preferences and alternative device designs, such as wearable patch injectors.

The study also revealed an unexpected twist. It showed that the negative effects of injection duration on users' forces was most pronounced in patient groups who exerted the least force to hold the device against the skin.* These patient groups, among them older female patients, are the most sensitive to the negative effect of the injection duration on the user's force, and thus show the lowest ability to withstand longer injection durations. Although dexterity, gender, age and injection experience have no overall impact on the ability to complete injections effectively, more nuanced effects at the patient group level need to be considered when designing future autoinjector devices. For example, the industry must be careful not to increase the injection duration for therapies to treat chronic disease states, such as osteoporosis, which specifically target older female patients.

SENSOR-AUGMENTED USABILITY STUDIES – A NEW STATE OF THE ART?

The study provides initial empirical evidence of the feasibility of longer injection durations using hand-held autoinjectors. Quantifying the effects of the injection duration on users' ability to hold the device against the skin during the injection demonstrates that extending the injection duration by one-second increments, on average, results in a reduction of the minimum user force of 1.3%. Additionally, these negative effects were most accentuated for patient groups, such as older female patients, who applied lower forces to keep the device pushed against the injection site.

Not only does the empirical research provide important insights into the feasibility of longer high-volume injection durations, but it also advances methodologically the study of patient behaviours during simulated-use studies. Researchers have only recently begun to introduce advanced sensor-augmented experimental methods to better characterise how participants engage with self-injection device technologies. As we continue to push the upper limit of injection duration with autoinjectors, we need to also keep pace with innovative methods to establish objective measures of how users self-administrate drugs – beyond the conventional endpoints of safe and effective use.

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"The study results provide initial empirical evidence of the feasibility of longer injection durations using hand-held autoinjectors."

ABOUT THE STUDY

The empirical study summarised here was funded by Ypsomed and conducted in collaboration with Design Science (Philadelphia, PA, US). As a leading developer and manufacturer of self-injection systems for subcutaneous drug delivery, Ypsomed has established a scientific research and communications programme with the purpose of advancing new insights that are relevant to industry and academia. The results regularly appear in peer-reviewed scientific forums, such as Expert Opinion on Drug Delivery and Medical Devices: Evidence and Research, and are presented at leading medical device and drug delivery conferences, such as the PDA Universe of Pre-Filled Syringes and Injection Devices.

ABOUT THE COMPANY

Ypsomed's comprehensive drug delivery device platforms consist of autoinjectors for prefilled syringes in 1 mL and 2.25 mL format, disposable pens for 3 mL and 1.5 mL cartridges, re-usable pen injectors, ready-to-use prefilled wearable patch injectors and injection devices for drugs in dual-chamber cartridges. Unique click-on needles and infusion sets complement the broad self-injection systems product portfolio.

With over 30 years of experience in the development and manufacture of innovative injection systems, Ypsomed is well equipped to tackle digital healthcare challenges and has strategically invested in the development of connected solutions and therapy-agnostic digital device management services. Anticipating the future needs of patients, pharmaceutical customers, payers and healthcare professionals, Ypsomed moves beyond manufacturing connected sensors. Ypsomed's smart device solutions strive to transform patients' lives by capturing therapy-relevant parameters, processing them to facilitate self-management of chronic diseases, and integrating these insights with third-party digital ecosystems. The company leverages its in-house capabilities in electronics, software and connectivity for the development of new devices and digital product systems.

Ypsomed is ISO 13485 certified and all processes comply with design control and cGMP guidelines with operational QA/QC experts on-site at each location. Ypsomed's FDA-registered manufacturing facilities are regularly inspected by pharma customers and regulatory agencies to supply devices for global markets including the US, Europe, Japan, China and India.

REFERENCE

1. *Schneider A et al, "Hold the device against the skin: the impact of injection duration on user's force for handheld autoinjectors". Expert Opin Drug Deliv, 2020, Vol 17(2), pp 225-236.*

**Linear regression models were built to assess the overall effect of injection duration on force applied to hold the device against the injection site. Quantile regression models were then used to show more nuanced effects of injection duration on the user's force. In particular, quantile regression revealed that the negative impact of injection duration on the user's force was most pronounced among participants who exerted the least force to hold the device against the skin, while it diminished for the higher quantiles.*

ABOUT THE AUTHOR

Andreas Schneider, PhD, is Innovation & Business Development Director at Ypsomed Delivery Systems. He leads a team that drives the definition and development of new drug delivery device platforms, such as next-generation pen and autoinjector devices, wearable patch injectors, connected systems and digital solutions. Dr Schneider has published various articles and given presentations in the areas of innovation management and drug delivery. He holds a PhD in innovation management and organisational sciences from ETH Zurich, Switzerland.

YDS YpsoMate® Zero

Zero carbon emission pre-filled autoinjector

- Zero carbon emission autoinjector offering without compromising on usability and patient safety
- Based on the proven 2-step pre-filled YpsoMate® autoinjector platform
- Use of alternative polymers for selected device components and packaging
- Close the loop for the packaging of device components and device sub-assemblies
- Offsetting the remaining carbon footprint with Ypsomed's own reforestation program

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