Human factors validation for a rheumatoid arthritis auto-injector for the adalimumab biosimilar FKB327

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Abstract: Rheumatoid arthritis (RA) is a chronic autoimmune disorder, often treated with adalimumab. This study was designed to validate usability of the adalimumab biosimilar FKB327 auto-injector (AI) and document risk associated with the device. A total of 136 participants were enrolled, including patients with RA, caregivers of patients with RA, and healthcare providers of patients with RA. Use errors and close calls were evaluated during 2 simulated injections. A full dose was administered by 90.4% and 97.8% of users for the first and second injections, respectively. The most common use errors were failure to squeeze injection site, check expiration date, check medication in viewing window, and rotate injection site during the second injection. The device, packaging, and instructions received favourable user ratings. FKB327-AI is an easy-to-use device for patients with RA, their caregivers, and healthcare providers. Errors that could lead to incorrect dose were infrequent and not associated with serious harm.

Keywords: adalimumab biosimilar; autoinjector; human factors validation; device usability validation; rheumatoid arthritis; rheumatoid arthritis caregivers; rheumatoid arthritis patients; safety analysis; simulated injections; user error analysis.

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1 Introduction

Rheumatoid arthritis (RA) is the most common autoimmune inflammatory arthritis among adults. RA causes inflammation of synovial lining and damage to joints and cartilage, which can result in severe and painful deformity and disability. Although RA primarily involves the joints, serious extra-articular manifestations include pulmonary involvement, vasculitis, and other systemic comorbidities (Smolen et al., 2016; Ostrowska et al., 2018). RA is increasing in prevalence, affecting approximately 1.36 million people in the USA (Singh et al., 2016; Helmick et al., 2008; Hunter et al., 2017).

In RA treatment guidelines, the American College of Rheumatology recommends initiating treatment with disease-modifying antirheumatic drugs (DMARDs) in newly diagnosed RA. For RA that is not responsive to DMARD therapy, injectable biologics – usually tumour necrosis factor (TNF) inhibitors – are the recommended therapeutic options. Several TNF inhibitors are now commercially available, including adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab (Singh et al., 2016). Biosimilars for the many anti-RA biologics are now coming to market, offering more options and cost-savings for consumers (Grewal et al., 2018).

Effective treatment with biologics requires long-term adherence to medication (Murage et al., 2018). Low adherence and non-adherence are associated with worse outcomes, underscoring the importance of interventions to improve adherence to biologic therapy (Bluett et al., 2015). One option for improving adherence is through self-administration, which eliminates the need for additional hospital visits and increases independence. Self-administration of biologics is correlated with higher patient adherence than provider administration, potentially leading to improved adherence and reduced costs (Schwarzenbach et al., 2014; Xiao et al., 2018; Dashiell et al., 2018; Schulze-Koops et al., 2015).

Treatments for RA can be self-administered using a variety of mechanisms, including prefilled syringes, syringes with vials, and auto-injectors (AIs). Compared with prefilled syringes, AIs are often preferred by patients because of the ease of use, convenience, time-savings, and safety of these devices (Paul et al., 2012; Kivitz et al., 2006). People who have an aversion to needles also prefer to use AIs over prefilled syringes (Stockl et al., 2007). Moreover, the hands and wrists are frequently impacted by RA, leading to hand deformities, reduced grip strength, lower coordination, and decreased dexterity (Figure 1; Erol et al., 2016). Therefore, easy-to-grip AIs may be preferred to syringes,

which require more coordination. Examples of AI features that have been designed with grip in mind include a surface that is not too slick or slippery and a diameter that is comfortable to hold in an adult hand. Thus, the usability of AIs is an important efficacy and safety consideration to avoid errors that could cause harm to end users.

Figure 1 Use of FKB327–auto-injector by a person with manual dexterity issues (see online version for colours)

Formal processes have been developed to characterise the types of errors and evaluate the frequencies of those errors during real-world usage, with the ultimate goal of creating products that are easy to use and safe (Medicines & Healthcare products Regulatory Agency, 2017). Use error analysis (UEA) is the process in which a user's tasks are broken down, and potential use errors during each task are identified during product design (Bligård and Osvalder, 2014; Hooper and Hitchens, 2011). Hooper and Hitchens proposed a method for identifying potential use errors in a user-centred fashion by integrating the user into the device system, performing detailed task and hazard analysis, and revising failure modes and effects analysis (FMEA) documents to incorporate those findings (Hooper and Hitchens, 2011). Their process estimated both severity and frequency of hazards, but regulatory requirements for usability validation place the most emphasis on the severity of potential harm. Our process reflected this and placed emphasis on critical tasks, which could lead to a high severity of harm if not performed or performed incorrectly. Once a list of predicted errors has been generated in the UEA, human factors engineering principles are then applied in a number of ways, including a usability test, in which end-users have the opportunity to interact with a device model in a simulated setting to detect use errors (Hegde and Respironics, 2013).

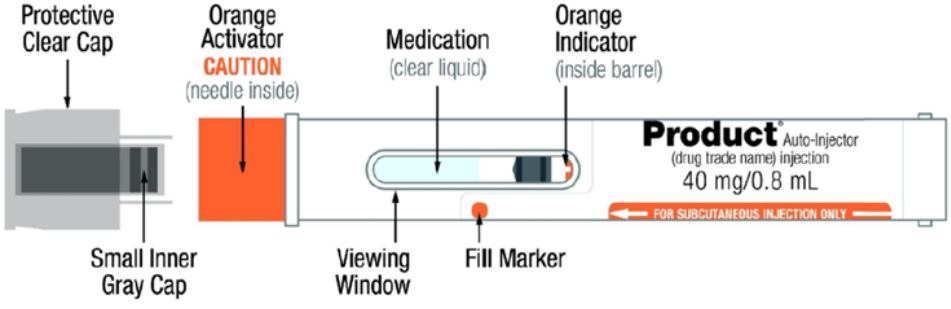
FKB327 is an adalimumab biosimilar that was developed to be administered using a biologic-device combination product (FKB327-AI) designed to deliver a single 40-mg subcutaneous dose of adalimumab. FKB327-AI is intended for self-administration by patients with RA, administration by caregivers of patients with RA, and administration by healthcare providers who treat patients with RA. The objective of this usability study was to evaluate the ability of representative end users to safely and correctly use the to-be-marketed FKB327-AI device and to assess the clarity and comprehensibility of the device instructional materials through simulated use and product knowledge questions.

2 Materials and methods

2.1 Study design

This study was an in vitro, non-clinical human factors validation study of the usability of FKB327-AI (Figure 2). Product usability was evaluated by simulating a typical product-use scenario for 3 end-user categories: patients with RA, caregivers of patients with RA, and healthcare providers who care for patients with RA, including nurses, nurse practitioners, and physicians. The study was designed and performed in accordance with the US Food and Drug Administration (FDA) Guidance for Industry, "Applying Human Factors and Usability Engineering to Medical Devices" (2016) and consideration of additional factors described in FDA's Draft Guidance Document entitled "Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development" (2016). This study was performed between March 23, 2016, and June 2, 2016. This research complied with the tenets of the Declaration of Helsinki and was approved by the New England Institutional Review Board (IRB #16-052). Informed consent was obtained from each participant.

Figure 2 Autoinjector schematic (see online version for colours)



2.2 Participants

Participants were representative end users aged 20 to 77 years who were recruited from the greater Providence, RI; Boston, MA; and Minneapolis/St. Paul, MN, areas. A total of 136 participants were enrolled: 60 patients, 61 caregivers, and 15 healthcare providers. Approximately half of enrolled patients and caregivers were injection-naïve. Patients and caregivers were categorised as injection-naïve if they had never given themselves or another person an injection using a needle and syringe, pen, jet, or related AI. Inclusion and exclusion criteria are described in Table 1.

2.3 Training

Patient and caregiver participants either received verbal and hands-on training by nurse educators (trained) or were untrained. All users were given the to-be-marketed version of the product in its intended packaging, including instructional materials, during the usability session. Trained participants completed their first injection a minimum of 60 minutes after training to simulate administration of the first injection, after leaving the

doctor's office, picking up medication from the pharmacy, and returning home. A planned distraction activity was introduced during the 60-minute window to interfere with training retention. All healthcare providers were untrained.

Table 1 Inclusion and exclusion criteria for all participants

Inclusion criteria	*Exclusion criteria*
All	
	• Being employed by, or living with someone employed by, a pharmaceutical company • The presence of serious health conditions that prevented participation • Inability to comply with the study schedule • Participation in an injection study in the past three months • Participation in a previous FKB327 formative usability or pilot study
Patients	
• Formal diagnosis of RA • Impairment of the hands, classified as mild, moderate, or severe	• Currently or previously employed as a healthcare professional • Low health literacy, defined as a REALM score <19, which corresponds to a reading level of grade 3 or below (Institute of Medicine Committee on Health Literacy, 2004)
Caregivers	
• Cared for patients with RA by helping with daily tasks at least one day per week	• Currently or previously employed as a healthcare professional • Low health literacy, defined as a REALM score <19, which corresponds to a reading level ≤grade 3 (Institute of Medicine Committee on Health Literacy, 2004)
Healthcare providers	
• Currently licensed and practicing healthcare • Involved in the treatment of patients with RA for at least one year prior to enrolment	

Note: RA indicates rheumatoid arthritis; REALM, Rapid Estimate of Adult Literacy in Medicine.

2.4 Usability sessions

The simulated-use scenarios for patients, caregivers, and healthcare providers evaluated tasks required for self-administration or administration of adalimumab. Patients and caregivers participated in two injection scenarios, simulating the adalimumab dosing schedule. Healthcare professionals performed the two injection scenarios in the same session but were asked to assume two weeks had passed between injection scenarios. All participants used fully functional AI devices filled with water for injection, which did not

contain active ingredients. Patients simulated self-administration into an injection pad attached to an area of their bodies of their choice. Caregivers and healthcare providers simulated patient administration into an injection pad attached to an injection area of their choice on a mannequin.

Table 2 Tasks and critical tasks

Task	*Potential clinical impact*	*Critical task*
Proper device storage[a]	Administration of ineffective, degraded, or precipitated drug and swallowing of movable part	Yes
Remove AI from device packaging	No treatment	No
Check expiration date	Administration of ineffective, degraded, or precipitated drug	Yes
Check medication in viewing window	Administration of ineffective, degraded, or precipitated drug	Yes
Select correct injection site	Intradermal or intramuscular drug administration	Yes
Wash hands	Microbiological contamination	No
Wipe injection site with an alcohol prep pad	Microbiological contamination	No
Remove AI cap	No treatment	Yes
Squeeze injection site to create a raised area	Intramuscular drug administration	Yes
Orient orange activator end toward injection site	Mechanical tissue irritation	Yes
Place AI at 90° angle to the injection site	Intradermal drug administration	Yes
Push AI down against the injection site so first click is heard	No treatment	Yes
Do not move, twist, or rotate AI during injection	Mechanical tissue irritation	Yes
Administer a full dose	Less than nominal drug volume administered	Yes
Pull AI straight away from injection site	Mechanical tissue irritation	No
Dispose of AI in a sharps container	Third-party exposure to non-sterile needle tip	Yes
Rotate and change injection site each time[b]	Mechanical tissue irritation	Yes

Notes: [a]Not evaluated during simulated-use scenario. Evaluated in product knowledge questionnaire.
[b]Evaluated for second injection only.
AI indicates auto-injector.

During the sessions, study personnel included a moderator and a data recorder in the room with the participant. All other study or sponsor staff observed tasks in a separate room through a one-way mirror. Audiovisual recordings of the usability sessions were made for later review, if needed.

All use errors and close calls were followed up with a postuse interview to determine how and why the participant believed the error occurred (root-cause inquiry). Participants were also asked to rate the ease of use of the product and the clarity of the instructional materials on a modified Likert scale.

Tasks required for safe and correct administration of drug with the AI were assessed in this study and are listed in Table 2. A participant's performance on each task was categorised as a success, success with close call, or use error. A use error occurred if a success was not reached. A close call was defined as a success that occurred after the participant

1 displayed confusion or hesitation in completing the task
2 omitted or improperly performed a step but corrected the use error and completed the task successfully
3 reported difficulty with the task and almost performed it incorrectly but corrected the error to complete the task successfully.

A subset of tasks was considered critical (Table 2), meaning the tasks could cause harm to the patient or user (including harm from compromised medical care) if performed incorrectly. Critical tasks were identified for the AI product using an advanced FMEA to assess the severity of risk to the user and patient, as well as any potential impact with respect to usability that may compromise patient care.

Participants also responded to product knowledge questions developed to evaluate aspects of use not conducive to simulated-use testing, including critical tasks such as proper device storage.

2.5 Data analysis

In addition to the aggregate data analysis, sensitivity analysis was performed to evaluate the occurrence of use errors among user groups; between injection-naïve and injection-experienced users; and between trained and untrained users.

3 Results

The characteristics of the study participants are summarised in Table 3.

3.1 Use errors

The most common use errors and close calls among patients and caregivers during the first session were use errors commonly related to injection device utilisation: squeeze injection site to create raised area (n = 49; 36.0%), check medication in viewing window (n = 31; 22.8%), and check expiration date (n = 31; 22.8%). The numbers of use errors and close calls for these tasks were reduced during the second injection task to 17.6%, 14.7%, and 18.4%, respectively (Figure 3). During the second injection, 57 users (41.9%) did not rotate the injection site. However, when questioned later, participants knew to avoid an injured area.

Table 3 Participant demographics

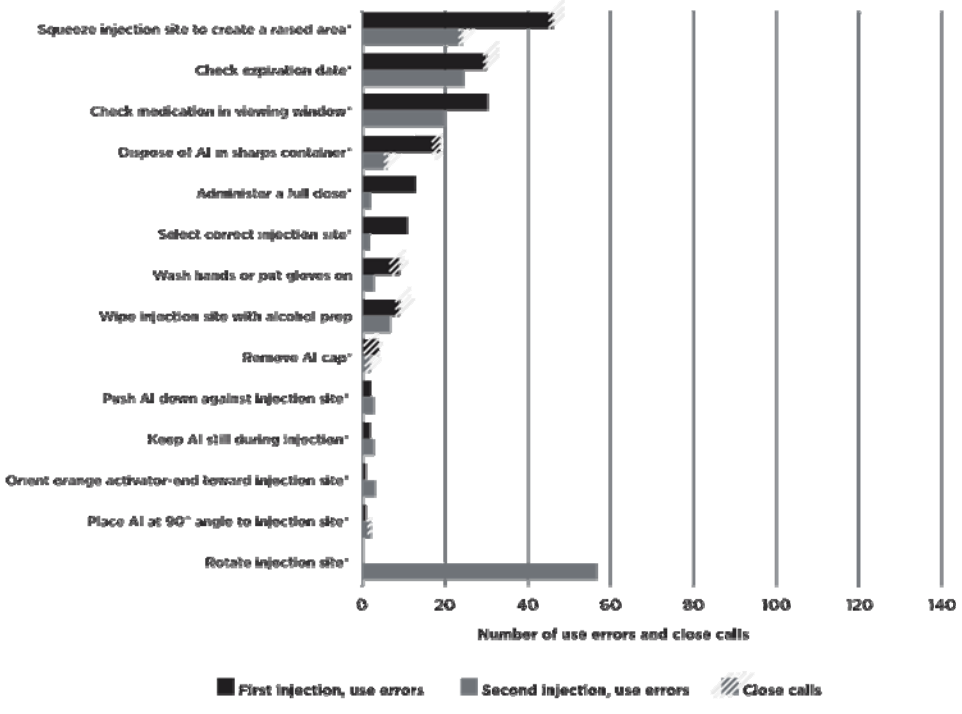
Characteristics	*Patients (n = 60)*	*Caregivers (n = 61)*	*Healthcare providers (n = 15)*
Age (years), mean (range)	54.4 (25–73)	47.1 (20–77)	49.6 (26–68)
Female, n (%)	41 (68)	37 (61)	11 (73)
Race, n (%)			
Black or African American	6 (10)	8 (13)	2 (13)
White	50 (83)	50 (82)	11 (73)
Other	4 (7)	3 (5)	2 (13)
Education, n (%)			
Some high school	1 (2)	0	0
High school	30 (50)	39 (41)	0
College	22 (36)	25 (41)	10 (67)
Postgraduate	7 (12)	11 (18)	5 (33)
Visual acuity, n (%)			
Perfect vision (corrected or uncorrected)	57 (95)	60 (98)	15 (100)
Imperfect vision (corrected or uncorrected)	3 (5)	1 (2)	0
Hearing loss, n (%)			
None	51 (85)	57 (94)	15 (100)
Mild	6 (10)	2 (3)	0
Moderate	3 (5)	2 (3)	0
Severe	0	0	0
Hand impairment from RA pain on day of usability session, n (%)			
None	0		
Mild	15 (50)		
Moderate	14 (47)		
Severe	1 (3)		
Days/week caring for someone with RA, mean (range)		4.5 (1–7)	
Years of experience treating patients with RA, mean (range)			10.5 (1–20)

Note: RA indicates rheumatoid arthritis.

During the first simulated injection session, 90.4% of participants administered a full dose; this proportion increased to 97.8% during the second simulated injection session. However, five participants (3.7%) erroneously administered two auto-injections during the initial injection. The risk profile of the biologic assessed the potential harm from this error as moderate. In addition, four use errors occurred because the device was temporarily left uncapped prior to injection.

When the rates of use errors were compared across groups, caregivers and patients had similar rates of use errors and close calls during the first and second injections. Each group had an overall higher rate of errors in the first session than in the second session. During the first injections, the rate of errors for untrained patients and caregivers was higher than the rate of errors for trained users; however, these rates were similar during the second injections. As expected, rates of errors were higher for caregivers and patients than for healthcare providers.

Figure 3 Instances of use errors and close calls during the first and second injection sessions for all end users (n = 136)



Notes: *Critical task.
AI indicates auto-injector.

3.2 Severity of use errors

The severity of potential harm from use errors ranges from a score of 2 to 10 (Table 4). The most frequent use errors recorded in this study were associated with various levels of severity. Failure to squeeze injection site is associated with a low level of severity (rating of 3), whereas failure to check expiration date or check medication in viewing window are associated with high severity (rating of 7). No use errors documented in this study were considered life-threatening.

Errors that led to potential underdosing or overdosing (e.g., failure to administer full dose, administration of 2 AIs) were relatively uncommon. These errors are of moderate severity and are unlikely to cause serious or life-threatening harm to the patient.

Table 4 Severity scale of potential harm according to the auto-injector AFMEA

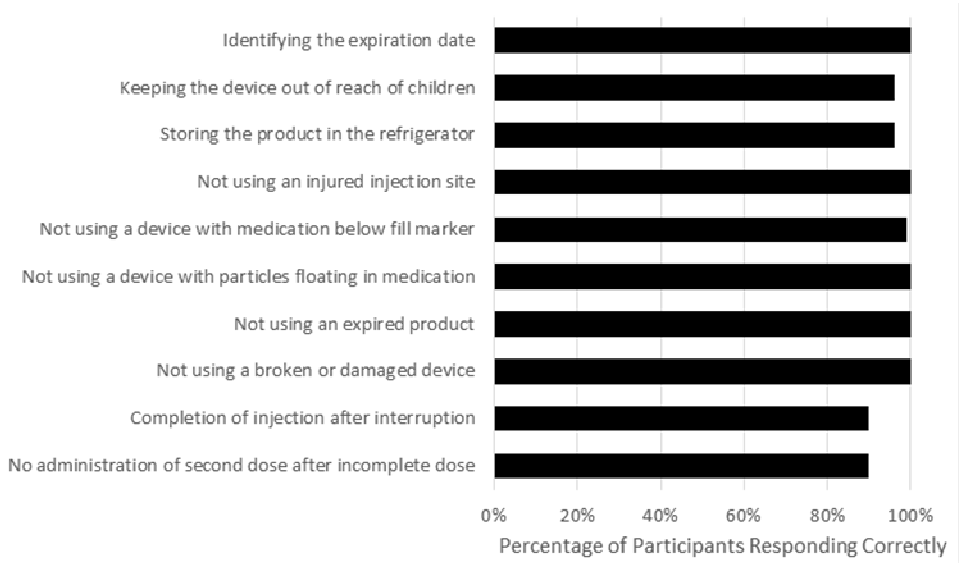
Rating	*Severity of failure*	*Harm to patient*	*Examples of use steps*
10	Very high	Death or serious deterioration of the state of health (e.g., shock, sepsis, loss of consciousness)	• Proper device storage
7	High	Persistent or strong discomfort (e.g., pain, allergic reaction, infection)	• Check expiration date • Check medication in viewing window • Select correct injection site • Orient orange activator end toward the injection site • Keep AI still during injection • Administer full dose • Dispose in sharps container
5	Moderate	Injury or impairment not requiring professional medical intervention (e.g., needle-stick injury with sterile needle)	• Wipe injection site with an alcohol prep • Remove device cap • Push the body of the AI down against the injection site • Hold AI to injection site until viewing window is blocked by orange and count to 10
3	Low	Inconvenience of temporary minor discomfort (e.g., local reddening of the skin)	• Squeeze injection site to create a raised area • Pull AI straight away from injection site
2	Very low	None	

Note: AFMEA indicates advanced Failure Modes and Effects Analysis; AI, auto-injector.

3.3 Product knowledge

Product knowledge was evaluated through a verbal knowledge assessment, including questions about the critical task of proper device storage. As shown in Figure 4, most users responded correctly to queries about various aspects of AI use. A total of 90% of users indicated that they would not administer a second dose when troubleshooting an incomplete dose. After consulting the instructions for use (IFU), the remaining 10% of participants correctly answered that they would not take the second dose. Similarly, 90% of users indicated that they would complete the injection after an unexpected interruption, and, after consulting the IFU, 8% correctly answered that they would complete the injection. The remaining 2% could not find anything in the instructions about this topic. The IFU also clarified proper storage for participants who incorrectly stated that they would not store in a refrigerator or would store within reach of children.

Figure 4 Product knowledge assessment



3.4 Subjective feedback

Participants were asked to rate the ease of use of the product and its accompanying instructional materials, as well as the clarity of specific topics described in the instructional materials. The responses to these questions are summarised in Figure 5. Overall, most participants stated that the IFU were very easy to use and very clear. The IFU included instructions on correct administration areas of the AI, which is important because the choice of injection site may impact successful completion of a subcutaneous injection.

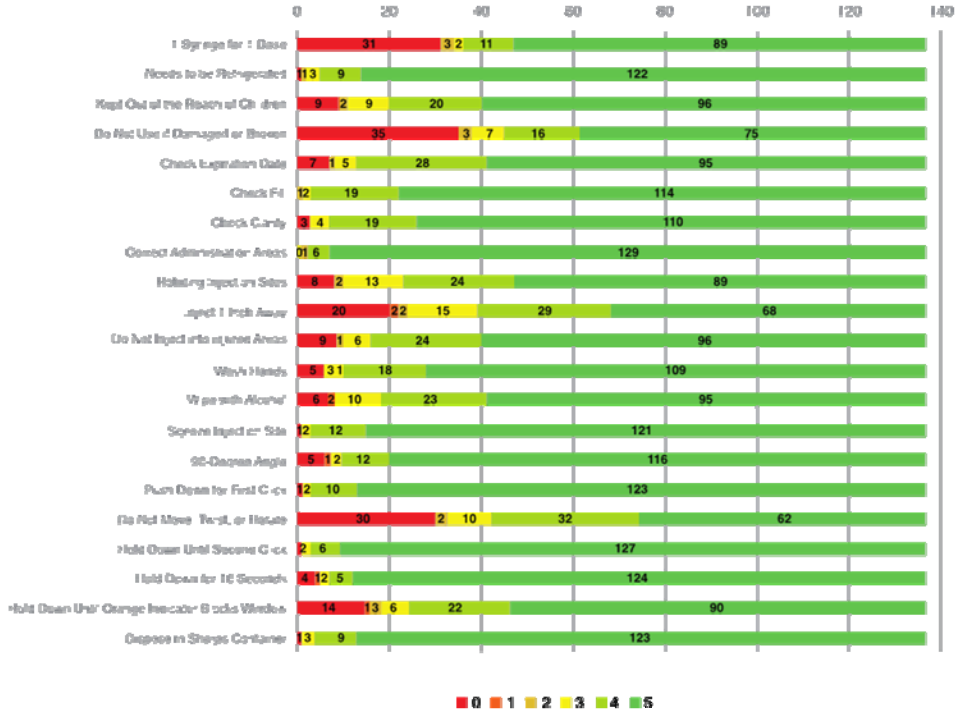
3.5 Adverse events

Two adverse events (AEs) occurred during the study. One patient pushed down on the orange activator and poked herself with the needle; however, she did not press down hard enough to activate the AI. She did not report a puncture, nor did she see blood. The AE resolved within three days. The second AE occurred when a patient oriented the AI upside down and activated it into the skin. The needle touched the skin; there was neither puncture nor blood. The AE was considered resolved immediately.

FKB addressed the risk for needle puncture due to improper orientation of the AI by applying additional on-device labeling to indicate the needle end of the AI and proper orientation to the injection site. These new risk-control measures were evaluated in a subsequent focused human factors validation study with 60 representative end users. No errors of improper orientation of the AI occurred.

Two serious AEs occurred during the study. Both were unrelated to the study activities and device and did not affect patient participation in the study.

Figure 5 Clarity of materials provided (IFU/QRG) (see online version for colours)



Notes: Subjective feedback was provided by all participants on a modified Likert scale from 1 (very unclear) to 5 (very clear). A score of 0 indicated "did not see in the materials provided."
IFU indicates instructions for use; QRG, quick reference guide.

4 Discussion

Medical errors are relatively common occurrences in the USA, with up to 98,000 deaths each year attributable to preventable medical errors (IOM Committee on Quality of Health Care in America, 2000). In addition to the cost to human lives, medical errors also are burdensome in terms of economic costs, morbidity, decreased treatment effectiveness, and decreased patient satisfaction. Errors are often caused by faulty conditions that lead to mistakes, underscoring the importance of careful product design to decrease or eliminate use errors. Furthermore, systems interventions, such as training on device utilisation, are key to improving usability (US Food and Drug Administration, 2016; IOM Committee on Quality of Health Care in America, 2000; Wittich et al., 2014).

In this usability validation study, the FKB327-AI device was shown to be used safely and correctly, with high rates of success by representative end users. Furthermore, the to-be-marketed materials were clear and easily understood. More than 90% of injections were completed successfully on the first try, and that percentage exceeded 98% with a subsequent try. Among the errors made by end users, most were of moderate or low severity. High severity errors (e.g., failure to check expiration date, select correct injection site, or dispose in a sharps container) were uncommon and were reduced in

frequency from the first to second injection. Furthermore, training from a nurse educator was associated with a lower rate of errors during the initial injection session. The rate of errors decreased from the first to the second injection, eliminating the disparities between trained and untrained individuals, and suggesting that, with practice, the FKB327-AI device is associated with a low residual risk for errors.

The patient and caregiver populations in this study had varied age, education, visual acuity, hearing loss, and disease-related symptoms, representative of a heterogeneous population of end users. Importantly, all patients had some level of hand pain when not receiving medication, and on the day of the session, half of all patient participants had moderate or severe levels of pain. The results of this study suggest that hand disability and deformity, as shown in Figure 1, are likely not barriers to proper use of FKB327-AI, an important characteristic for anti-RA drugs. The haptic features of FKB327-AI that improve its usability among patients and caregivers with hand pain include a non-slippery body, an optimal diameter of 18.2 mm, low trigger force without need to press a button, and a non-slippery needle cap for gripping. Future studies could include evaluation of a population enriched for older patients with severe disease, hand disability, and/or frailty to confirm these findings.

Critical tasks for the proper use of FKB327-AI are those that could result in either a high severity of harm or in compromised medical care (e.g., no treatment). Because of the preponderance of critical tasks, most use errors and close calls documented in this study occurred during performance of critical tasks. Failure to successfully complete critical tasks had a range of clinical implications, from microbiological contamination to administration of ineffective, degraded, or precipitated product. Although these errors could result in impairment or persistent discomfort, none of the errors identified were life-threatening. Indeed, the only critical task identified as potentially life-threatening in the case of failure was improper storage of the device within reach of children, due to the risk for swallowing parts. The vast majority of participants were able to correctly explain that the device should be stored out of reach of children.

Potential device-specific errors (e.g., failure to remove cap or failure to orient device properly) occurred very infrequently. Most errors that occurred in this study are common to self-injection processes and have been reported in previous usability studies of other AI devices. Of the 13 categories of use errors observed in the present usability study, 12 were previously reported in other studies of AI device usability, according to the results of a systematic review that analysed the results of 38 studies and 232 use errors and close calls. Only failure to rotate injection site was not reported as an error in the systematic review; however, no data about a second injection were discussed, suggesting that this task may not have been evaluated in any of the reviewed publications (Weinhold et al., 2018).

A benefit–risk analysis of FKB327-AI has also been performed, and the low proportion of device-specific use errors and close calls is likely attributable to several user-focused FKB327-AI design features. For example, FKB327-AI has a one-step activation process that eliminates the need for priming and activating the device; users simply have to place the device against the injection site and press down to initiate the injection. Furthermore, the AI requires low trigger force to activate the needle and the body has an easy-to-grip, non-slippery exterior. This feature is likely particularly beneficial for patients with RA who have hand or wrist disability or deformity. The three feedback indicators for full dose delivery are audible clicks, orange indicator in the viewing window, and length of time since the start of the injection. Device labelling was

added to clearly indicate the needle end, whereas outer and inner packaging were developed to be easy to use. Furthermore, risk mitigation factors were applied to prevent needle puncture (additional labelling), and a subsequent study supports the success of those features, as no incidents of incorrect device orientation or needle punctures occurred in that study. After these and other design and labelling risk mitigations, residual risks have been determined to be non-specific to the FKB327-AI, and additional risk mitigations were not expected to further reduce errors. The results of the present usability validation study support the findings of this benefit–risk analysis and are suggestive of few residual product-specific risks.

5 Conclusions

FKB327-AI is an easy-to-use device with clear packaging and instructional materials. The device and its materials were associated with few device-specific errors and no use errors leading to life-threatening or serious harm. Errors that led to administering an incorrect dose were infrequent, not associated with potentially life-threatening or serious harm, and largely corrected after administering the first dose. The results of this study further support the results of a previous benefit–risk analysis, which showed that the design of the FKB327-AI leads to safe and correct use by end users, and the benefits of the FKB327-AI outweigh the residual risks associated with its use.

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