Molly® Autoinjector

A Systematic Review of Molly's Integrated and Flexible Device Design and Development Model

SHL MEDICAL

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Molly®
Modular
Platform Technology

Introduction

Injectable drug delivery systems have become an important and integral part of modern medicine, owing to various key drivers such as human health and well-being, drug development and delivery, and patient compliance, safety, and usability.

Experts estimated that the prevalence of chronic diseases would increase from 46% to 57% between 2001 and 2020. The US Centers for Disease Control and Prevention define chronic diseases as "conditions that last one year or more and require ongoing medical attention or limit activities of daily living or both". Chronic diseases have often been linked to patient disability and mortality, including cardiovascular diseases, diabetes, and cancer, to name a few. The burden of chronic diseases continues to grow, and the need for reliable patient therapies is imminent.[1, 2]

At present, an increasing focus of drug therapy is self-administration, mainly due to the added benefits for patient convenience and compliance. In addition, the focus on self-treatment in order for chronic disease patients to avoid hospital visits has been highlighted by recently discovered infectious diseases like COVID-19. Therapeutics that allow for patient self-administration can be delivered via devices like pen and autoinjectors as well as prefilled safety syringes.

The growing pipeline of biologics and biosimilars helps enable the adoption of self-administrable injection devices, and this adoption is increasing. Looking at relevant numbers, the period of 2014 to 2018 saw at least 129 regulatory approvals of recombinant biologics. In 2020 alone, the US Food and Drug Administration (FDA) approved 53 novel drugs. Of these, 26 were medicaments developed into injectable formats, with at least five currently available as subcutaneous injections. Interestingly, target disease indications for these combination products include the likes of rheumatoid arthritis, psoriasis and other related arthritis diseases, multiple sclerosis, and diabetes – all of which are chronic disease states.[3, 4, 5, 6]

For patients with chronic conditions, drug delivery systems like pen and autoinjectors offer distinct advantages over traditional syringes – and these advantages fall into operational utility, patient safety, and usability. Government regulations have been expanded in recent years to provide more comprehensive guidance for medical device designers in developing safe and effective delivery devices for patients.

EPIDEMIOLOGICAL DEFINITIONS

Chronic diseases are defined as conditions that last one year or more and require ongoing medical attention or limit activities of daily living or both.

Prevalence refers to the proportion of persons who have a condition at or during a particular time period.

A BRIEF HISTORY OF HUMAN FACTORS & USABILITY ENGINEERING

Although there were earlier published guidances on human factors design process for medical devices (see ANSI/AAMI HE48:1993, ANSI/AAMI HE74:2001), it wasn't until 2007 when the first harmonized standard on the application of usability engineering to medical devices was published (see IEC 62366:2007).

Background and Objectives

While one of the first "modern" prefilled autoinjectors received regulatory approval in 1987 (i.e., the EpiPen), it wasn't until the 2000s that medical device development saw increasingly clear and harmonized regulatory guidance regarding the important application of human factors and usability engineering.
In fact, the first harmonized standard on the application of usability engineering to medical devices was published in 2007. In 2011, the US FDA updated its current thinking on the increasing importance of the patient experience of handling medical devices by conducting usability studies to maximize the likelihood that devices will be safe and effective for the end users. The updated guideline draft came a decade after its predecessor, which had been released in 2000. The final version of this guidebook, titled "Applying Human Factors and Usability Engineering to Optimize Medical Device Design", was published in 2016, marking the introduction of higher expectations for ensuring a better medication-related experience for users.[7]

SHL Medical's Design Thinking and Engineering Process Enable Molly's Technology

Using a timeline analysis to understand the development of design thinking and engineering at SHL Medical (Figure 1), we find that SHL adopted a user-centered design thinking approach even for its first device project. SHL's focus on the principles of design engineering was instituted early in its operations, with its first autoinjector project initiated under a dedicated team of industrial design experts. Now, this foresight to design devices that address the unmet needs of patients extends to every device project happening in parallel under SHL's complex operations. Consistently, SHL's main objective has been to design patient-centric devices.

DESIGN THINKING

Design thinking is an iterative process and user-centric approach wherein one prioritizes developing empathy for users, working in collaborative multidisciplinary teams, and adopting the action-oriented rapid prototyping of solutions.

DESIGN THINKING VERSUS HUMAN-CENTERED DESIGN

Various references outline design thinking and human-centered design (also called user-centered design) as highly interrelated, and sometimes interchangeable according to context. A 2019 report states that "Design Thinking is a *human-centered approach* to solving complex, ill-defined problems".[8]

In 1995, SHL worked on its first internal device project, led by its in-house design engineers and developed the device functionality with inputs from healthcare professionals who work with the intended end users. At a time when the medical device industry focused more on device functionality, SHL's approach involved early in the process the intended end user: the patients. For example, the device design for this particular project took the form of a fountain pen so that users could manage the treatment discreetly and with a level of elegance. This, in turn, was well-received by the pharma partner as well as the patients during that time. In 2000, the US FDA then published its regulatory guidance titled "Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management" effectively replacing its draft guidance published a year earlier.

SHL MEDICAL'S DESIGN CENTERS AT A GLANCE

At present, SHL Medical has established a total of 4 design centers situated in Sweden, USA, Taiwan, and Switzerland.

Over the years, SHL Medical has been proactive in incorporating design thinking and engineering in its device development process. A continual demonstration of this practice would result in the establishment of SHL design centers in Sweden and the USA (2004), Taiwan (2011), and recently a design center in Switzerland. All these activities were established gradually in-house, as opposed to outsourcing from any external business partner. SHL Medical's design engineering process built over time has continually supported the development of its device solutions for pharma partners – including the first iteration of the Molly device empowered by the Molly technology.

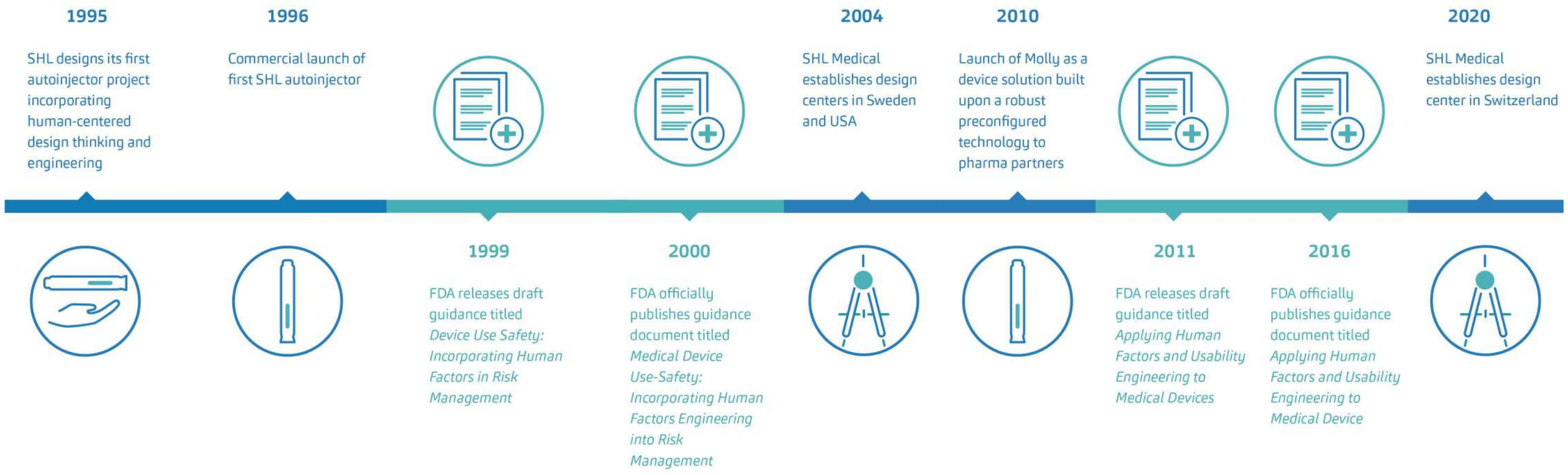

Figure 1: Timeline representation of SHL Medical's hallmarks in design engineering in relation to US FDA guidance on human factors and usability engineering for medical devices.

ERGONOMICS OF THE MOLLY AUTOINJECTOR

Molly is a 2-step device that features automatic needle insertion upon pressing the autoinjector against the skin. An audible "click" sound will occur upon device activation along with a second click near full injection of the drug.

The Molly Design and Usability Methodologies

In recent years, experts in the medical device field have stressed the importance of human-centered research and development in the field of medical technology. A 2019 report by thought leaders in the medtech space contextually defines design thinking as a human-centered approach to solving complex, ill-defined problems. Further, they explain that design thinking serves as a robust anchor to what is called context-driven development, where medical devices should be designed and developed with users' needs and experience on top of the device developer's mind.[9, 10, 11]

In 2010, the first iteration of the Molly device enabled by the Molly technology was presented as a device solution to pharma customers. Looking back at a time when biologics development was on the rise, a preconfigured device solution was imminent to address the requirements of pharma, the medicament, and patients alike. From a device solution for combination product development, Molly saw its first commercial launch in 2015 as part of a combination product for rheumatoid arthritis. Interestingly, between 2015-2016 alone, the Molly technology had supported the regulatory approval and commercial launch of at least four combination product projects under SHL Medical's pharma partners.

At present, the Molly technology has enabled various commercially marketed drug-device combinations, all of which constitute the Molly family of devices. As a patient-operated drug delivery system, each device must ensure the safe and effective delivery of the drug to the end user. The essence of a patient-centric device, as has been outlined in design control regulations by the FDA, lies on evidence that it has been designed and developed to meet end user needs and requirements.

A Human Factors Study conducted with SHL Medical's research partner in 2018 (Figure 3) reveals the merits of the device design found in the Molly autoinjector. To vet the operational usability of the device through an experimental design, device-naive participants representing various medical conditions were given a Molly autoinjector to use and were then asked to rate the ease or difficulty of operation. Briefly, results indicate relative ease of operation for most participants.

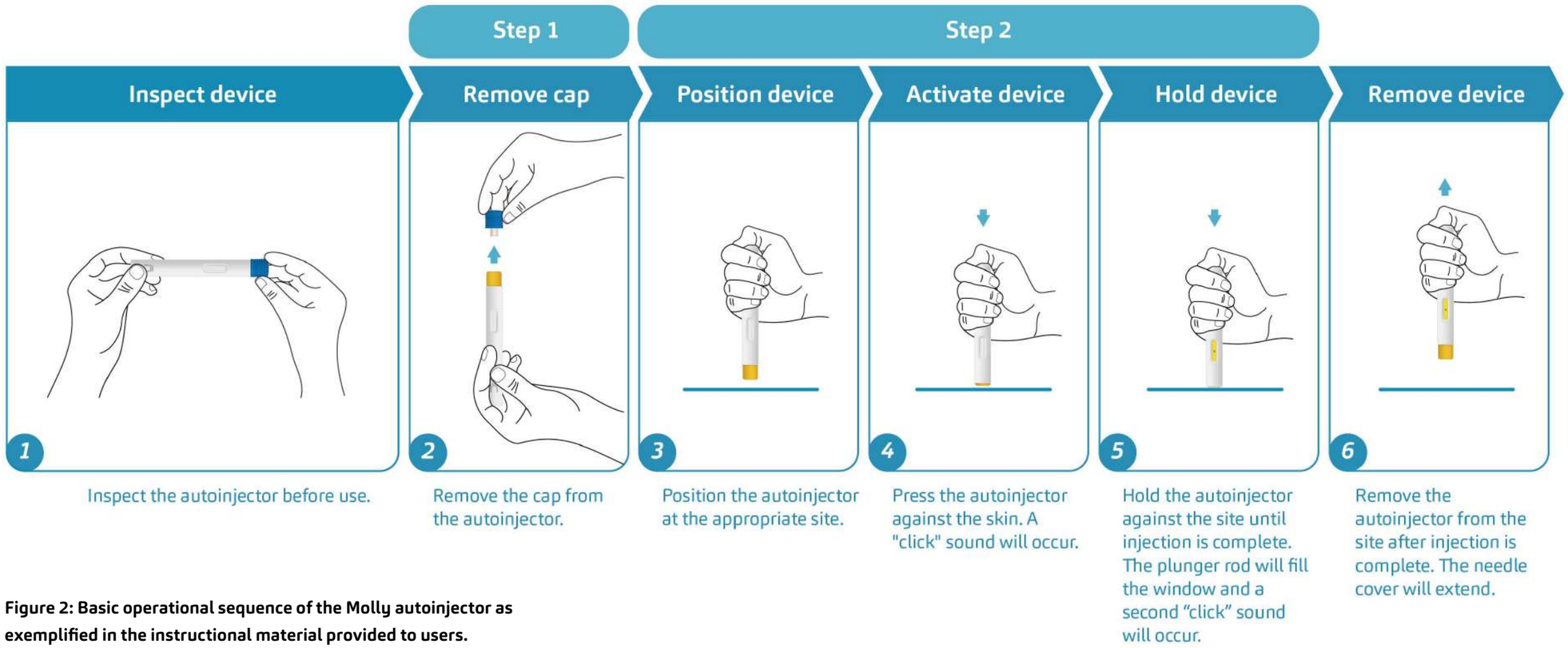

Figure 2: Basic operational sequence of the Molly autoinjector as exemplified in the instructional material provided to users.

PARTICIPANTS

Age	Females	Males	Impairments			Medical condition (#)	
			Visual	Auditory	Dexterity		
18-30	0	1	0	0	0	High cholesterol (8)	None (3)
31-40	1	2	0	0	0	Dermatitis (3)	Rheumatoid arthritis (2)
41-50	1	0	1	0	0	Diabetes (1)	Ulcerative colitis (1)
51-65	3	0	3	0	0	Multiple sclerosis (1)	
66 +	2	4	6	2	1		

After using the autoinjector, participants rated the ease or difficulty of the following actions:

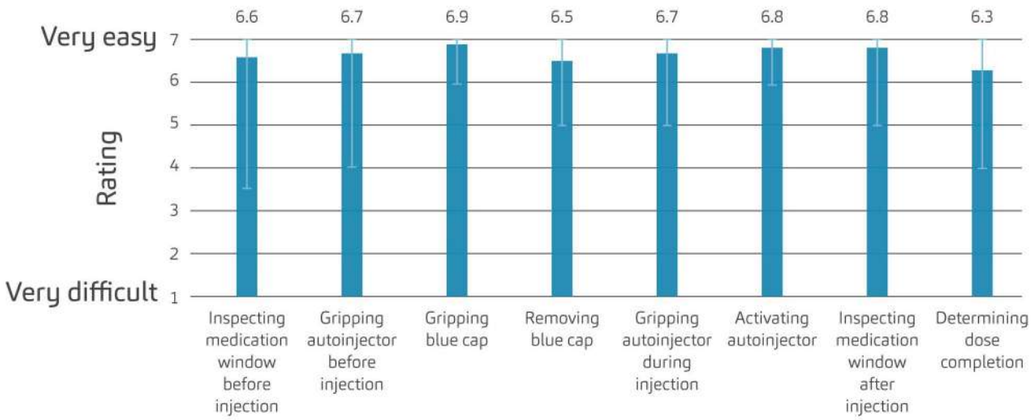

Figure 3: Statistical summary of a Molly Human Factors study conducted in 2018.

DEVICE NAIVETY IN HUMAN FACTORS STUDIES

In the experimental design of usability testing of autoinjectors, device naive participants refer to individuals without prior knowledge and exposure to the device under study. This prevents operation familiarity and bias with a certain device in question.

In summary, the study highlights how the design engineering and usability process for Molly has responded to the requirements of relevant stakeholders. Based on all the positive test results, a design improvement is not warranted for the device to successfully function. While the study does not draw insights from a highly specific user group and disease state, it was able to meet its objections such as:

(1) identify any design shortcomings that could lead to potentially harmful use errors; and,

(2) collect users' feedback regarding the device's strengths and opportunities for improvement.

Test-Based Feasibility Studies, Design Assessment, and Design Verification Processes to Fulfill End-User Needs

In autoinjector development, a holistic device design process is critical to ensure that all stakeholder inputs and end user needs are addressed. To accomplish this, a robust design control process must be established, specifically under the requirements outlined by regulations such as the US FDA CFR 820.30 and the harmonized Quality Management Systems (QMS) standard for medical devices ISO 13485. This systematic approach ensures that user needs are contemplated by design input requirements and, in turn, that the autoinjector performance meets the design input requirements. Within the design controls process, certain stages are required. These stages are noted in Figure 4 below. In essence, SHL Medical is involved in the design review processes until which the design validation phase is undertaken by the pharmaceutical partner.

DESIGN CONTROLS AT SHL MEDICAL

SHL's Design Assessment and Verification activities were developed in response to the requirements outlined by regulations such as the US FDA CFR 820.30 and the harmonized Quality Management Systems (QMS) standard for medical devices ISO 13485. Refined over the years, SHL's approach to design controls revolves around a cascade of activities that accompany the device development process as the design matures rather than be purely a stage-gated approach.

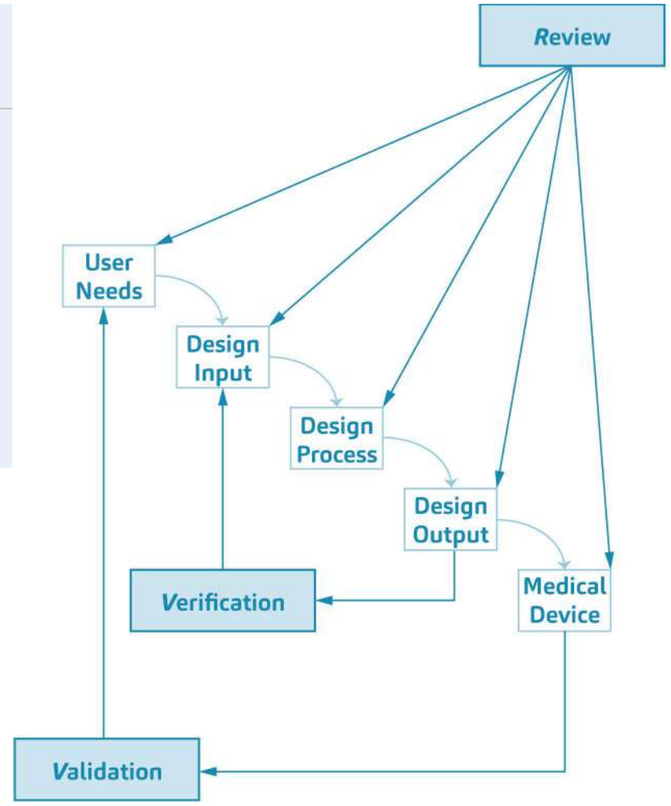

Figure 4: The US FDA 820.30 Design Controls Flowchart. ***Figure is not intended to imply that the full scope of the aforementioned FDA regulation is performed by SHL Medical.***

DESIGN ASSESSMENT

Design Assessment at SHL Medical refers to the series of tests performed along the device design and development process to understand the performance and limitations of the device design.

As noted in Figure 4, SHL performs multiple checks and reviews during the development of an autoinjector. While documentation reviews of quality requirements, functional performance requirements, and other related items are performed throughout the development of an autoinjector, the autoinjector's conformity to critical performance characteristics is confirmed by performing robust functional testing under challenge conditions outlined by the various appropriate ISO requirements (ISO 11608-1, ISO 11608-5, etc.). According to SHL Medical's internal procedures, these challenge tests are conducted in two phases, namely, the Design Assessment phase and the Design Verification phase. Figure 5 below exemplifies that SHL's design control activities are mutually inclusive and have been designed to support the whole device development process rather than be purely a stage-gated approach.

The first functional performance confirmation is an initial assessment of the device from the standpoint of an engineering study. Certain worst-case challenge tests are performed to ensure that the device performance meets the intended requirements as contemplated by the original design inputs.

DESIGN VERIFICATION

Design Verification refers to the series of tests aimed at understanding the performance of the device components or sub-assemblies such that functional errors of the autoinjector may be corrected and occurrences of such errors (as they may arise from the production process of the device parts) be mitigated/eliminated.

The second testing regime is the Design Verification phase. During this testing, the full scope of challenge tests and functional performance characteristics are studied and documented. After successful completion of testing, these data are then submitted to the pharmaceutical partner who then submits the data as part of their combination product dossier to the respective regulatory authorities for review.

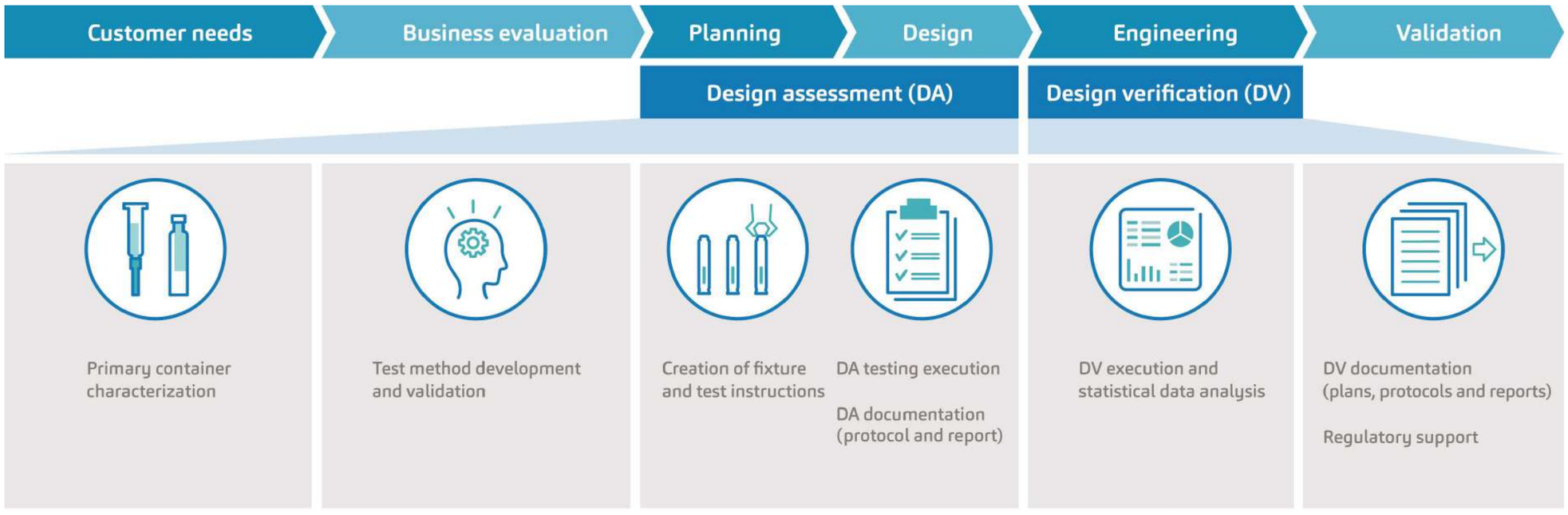

Figure 5: A standard suite of design controls ensures that the Molly device meets the required characteristics.

LEVERAGING HISTORICAL LEARNINGS

Years of iterative testing of the platform-based Molly device technology has allowed SHL to leverage design knowledge learned over the years and apply these learnings on succeeding Molly device projects. SHL Medical's Molly device projects draw upon historical data to prevent redundancy along the device development stream.

Through this approach, Molly-based device development projects of varying levels of customization leverage the modular platform infrastructure that supports the robust Molly technology. This mature device technology allows for an intensive but time-saving approach by identifying the relevant tests required through a process called *applicability assessment*. With a mature device technology, applicability assessments performed on each device project would identify the relevant testing parameters and expected test results, allowing for an informed progression along the project.

When we talk about a highly customized Molly device project, although the design prototype of all Molly-based devices will have to undergo formative and summative studies, the modular platform approach allows a level of reliability by ensuring that customized parts are assessed early in the design review phase. Device projects that entail a high level of customization include instances where there is a need to change the geometry of the autoinjector cap and/or body.

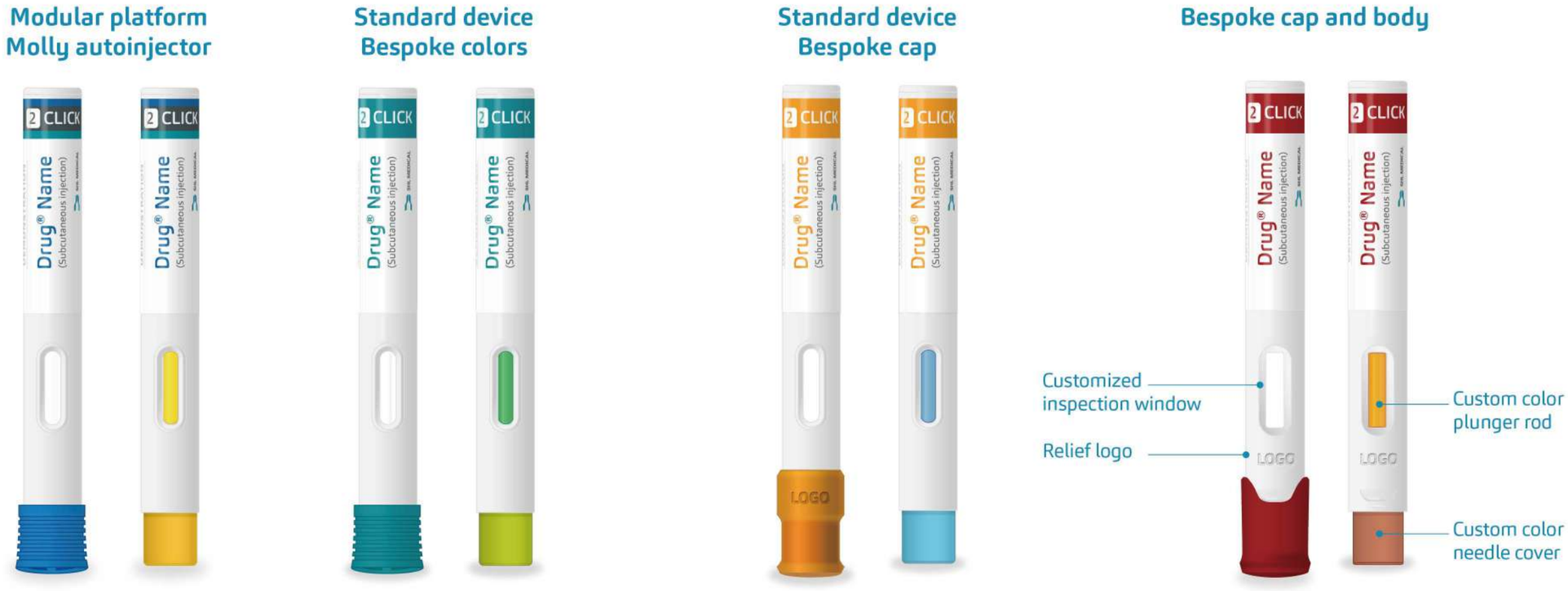

Figure 6: A range of possible customizations enabled by a modular platform technology.

LEVELS OF CUSTOMIZATION

SHL provides several levels of customization through Molly's modular platform technology, with options ranging from change of cap and needle cover color, to change of cap shape and the ability to select from among preset viewing window sizes, or even using a completely different design with the same rotator-based device mechanism.

To support customized Molly device projects, test engineers develop and validate test methods that are in accordance with international standards, such as ISO 11608. In terms of hardware, automation experts support the development of versatile testing fixtures integrated with SHL-built add-on equipment. These multi-component machines function as discrete units capable of measuring cap removal force, activation force, injection time, dose accuracy, and needle extension.

Of important note, these feasibility studies and design assessment activities are initiated in the early development phases of a device project. This means that an informed characterization of the device design happens early, mitigating further risks and failures downstream of the device development process.

02

MANUFACTURING SCALABILITY THROUGH A STREAMLINED & MODULAR DESIGN APPROACH IN MOLLY DEVELOPMENT & PRODUCTION

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PRODUCT LIFECYCLE MANAGEMENT

Lifecycle management is the process of managing a product's lifecycle from inception, through design and manufacturing, to sales, service and eventually retirement.

Introduction and Background

For a combination product project, the entire lifecycle management does not end on meeting production for clinical needs. With consideration for an eventual regulatory approval and market launch, scalable production capacities are essential to ensure that manufacturing volumes meet the medical needs of each and every intended patient group. Equally, a device project must be manufacturable through infrastructures that ensure economic costs and short development timelines.

For projects built upon the Molly technology, a modular design approach not only on device components but also in production allows for customization requests from customers. The core technology, which includes fewer than 15 components, reflects critical considerations of design for manufacturing and assembly (DFMA) concepts. According to Siemens, DFMA is defined as "an engineering methodology that focuses on reducing time-to-market and total production costs by prioritizing both the ease of manufacture for the product parts and the simplified assembly of those parts into the final product – all during the early design phases of the product lifecycle".[12]

Here, the focus on DFMA concepts integrated with patient-centered design makes the Molly technology both robust and flexible, allowing for industrial design options and also manufacturing scalability – supporting market differentiation and short development timelines. For SHL Medical, design and process development teams collaborate early in the product design development process, working in parallel across operational teams during the planning and design phases.

A Robust Device Design Built Upon Modular Components

There is little empirical evidence for distinguishability of look-alike self-injection devices among its users, and thus patient handheld devices based on the same technology must provide design customizations for differentiation. This imperative can be seen in a recent device-related European Medicines Agency advisory published in 2018. Using a retrospective analysis of Molly device projects, the maturity of the platform device technology has enabled the customizations found in subsequent Molly bespoke projects. Of important note is that both the 1.0 mL and 2.25 mL standard versions of the Molly autoinjector reflect a modular approach in their core design technology.[13]

MODULARITY OF A PLATFORM EMBEDDED WITHIN THE DEVICE

In the tangible sense of things, the Molly autoinjector is modular in that both front and rear sub-assemblies comprise five to six intricately designed parts that make up the preconfigured aspect of the device technology.

For instance, the Molly device technology is modular in the sense that both the front and rear sub-assemblies comprise five to six intricately designed parts. This preconfigured technology allows an appreciable level of freedom for customization while maintaining its rotator-based mechanism.

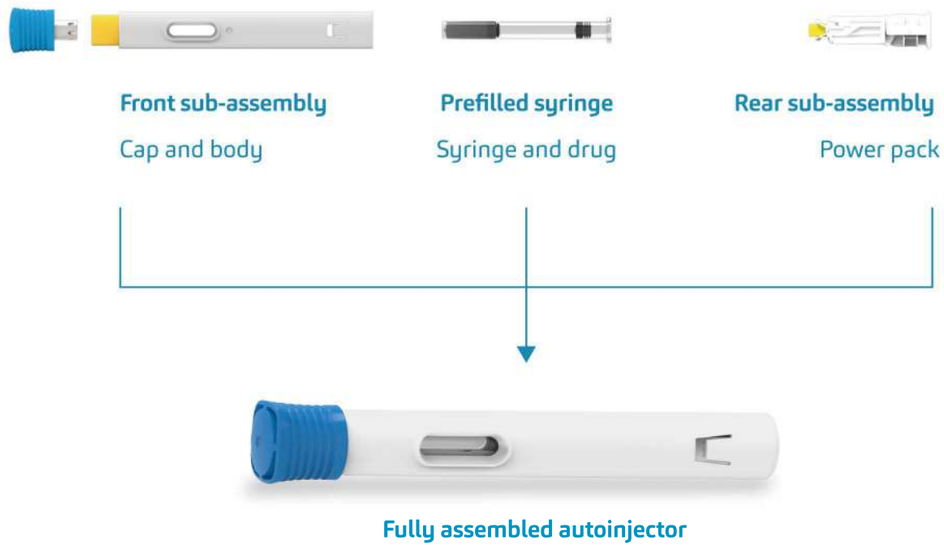


Figure 7: A simplified representation of the Molly autoinjector technology built upon the modular front and rear parts and sub-assemblies (syringe included).

With front and rear modules comprising its integral platform components, Molly enables design feature modifications to differentiate a device's appearance. For instance, the color of the cap, needle cover, and plunger rod can be changed. Aside from these, device body customizations not only for branding and market differentiation but also for patient distinguishability are possible. Semantically, this reflects a concept of structural polymorphism wherein for Molly device projects, the core technology components always remain intact while a degree of customization may be seen in its industrial design.

Extensive experience with Molly projects also translates into the parallel maturity of infrastructures that support the design and development ecosystem of such device projects. With a device technology built upon standard modules and mature infrastructures, Molly supports customized solutions according to drug, pharma, and patient requirements.

SIMULATION STUDIES AT SHL MEDICAL

Flexibility in process development is key to enabling customizations in device offerings. At SHL, process development is an overarching stream that safeguards the manufacturability of the device, and SHL performs simulation studies throughout the engineering feasibility phase as well as DFMA studies to ensure that the device's design input requirements (DIR) are met.

A Vertically Integrated System Enables Streamlined Communications and Synchronous End-To-End Processes

Just as intra-organizational communication is important in the field of healthcare, medical device development also considers this as an important element within its end-to-end procedures. In contrast to a linear device development process, Molly autoinjector projects are supported through an array of in-house capabilities, resulting in a parallel development process. These in-house capabilities ensure a vertically integrated system at SHL Medical, enabling various product development activities to have parallel, overlapping timelines. Clear evidence of this is the establishment of process development from planning through to the validation stages of an SHL device project (see Figure 9). Subsequently, this vertical integration of core capabilities enables intra-organizational communications wherein technical information can be relayed directly and effectively. Using this model, the risk of communication failure is minimized. Likewise, feedback can be provided efficiently, limiting process errors (as depicted and described in Figure 8).

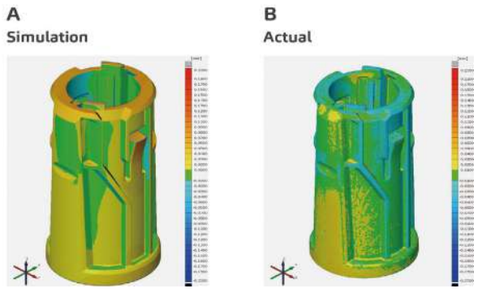


Figure 8: Vertical integration of device development processes allows SHL to minimize or limit process errors. Detecting problems in early simulations of a Molly device part means that the root causes are rectified first to ensure actual part production stays within specifications.

For example, desirable results in early simulation tests of a Molly sub-assembly will mean that the project will proceed to the next step, otherwise the root cause shall be investigated to ensure that the actual part production done at a later stage meets the required device part specifications. While various organizational models suffer from asynchronous communications, the vertical integration of product development capabilities enables SHL Medical to be streamlined. This presents a considerable improvement in logistics management and helps reduce the lag and idle time that occur with stepwise operations.

An Overarching Process Development System to Translate Design Specifications to Product Specifications

Given the complexities of device development for combination products, the vertical integration of in-sourced capabilities offers a systematic workflow for product and process development solutions. While most organizations start process development work at the interface of a device project's design and engineering phases, the process development system at SHL Medical overarches all stages of a project. This means that Engineering Leaders (process engineers) are assigned and involved early in the official adoption of each pharma partner's device project. Through this system, Project Managers and Design teams can work closely, not only with Development and Engineering (DE) teams but also with Process Development (PD) teams during the design phase, to develop a design proposal that meets end-user requirements. An overview of SHL Medical's overarching process development streams is visualized in Figure 9.

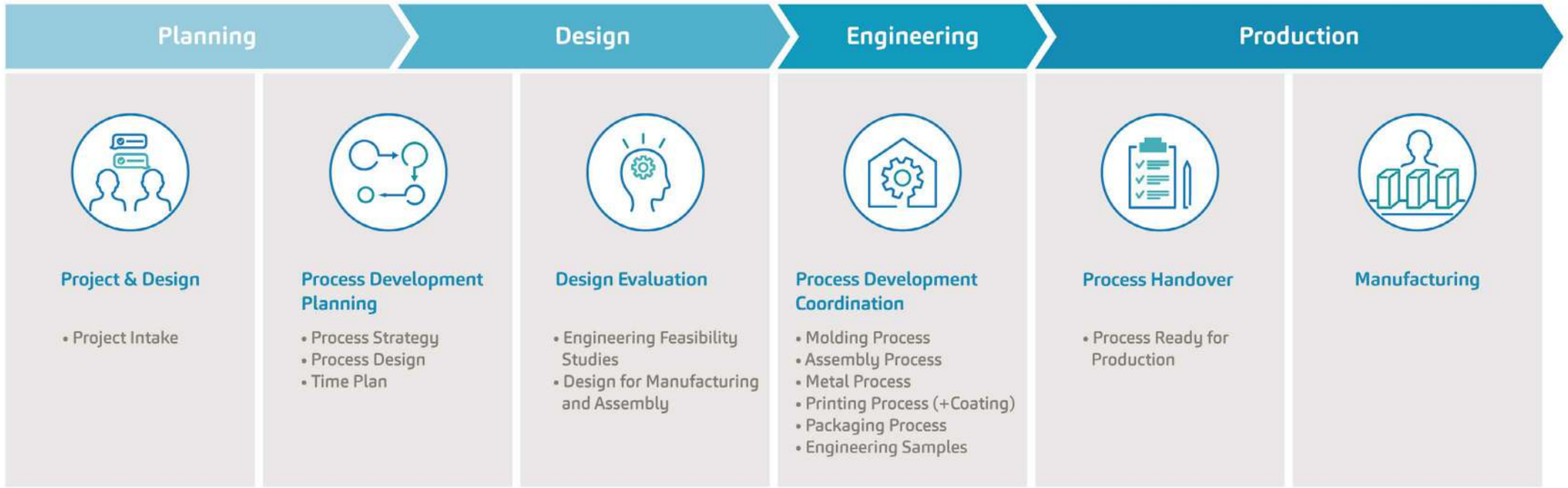


Figure 9: SHL Medical's overarching process development streams. The validation phase and final assembly are not shown in this figure.

A Scientific- and Engineering-Based Approach to Design for Manufacturing and Assembly

Aside from a robust device technology that enables Molly, how is production scalability guaranteed for Molly device projects of varying design customizations? While design for manufacturing and assembly (DFMA) concepts are not new, the process development structure at SHL Medical continuously adapts a scientific- and engineering-based approach to DFMA. As a systematic solution to bespoke Molly projects, DFMA evaluation is carried out at the earliest practicable stages of product design.

An important highlight of this system is that DFMA concepts are explicitly outlined during the design proposal step in preparation for a device project's engineering phase. This ensures that tools and process flow are well-coordinated and integrated with mass production requirements as well as capabilities, ultimately supporting the original device design requirements.

For example, a Molly device project will undergo stringent reviews during its design phase by various subject-matter experts, well before it enters the mass manufacturing stage. This would include:

1. A review of the input materials, such as the plastic and metal components to be used throughout the manufacturing process
2. Injection molding and assembly simulations by computational engineers
3. Molding and assembly process reviews in accordance with historical data, or prior knowledge from similar projects
4. Toolset reviews of mold structure by tooling experts
5. Reviews by process and automation experts of the assembly process as well as equipment considerations for mass production

In brief, various experts are sought to ensure that the manufacturing stream is guaranteed. This system, along with the mature Molly technology, improves manufacturability and mitigates project risks in relation to the impact of design changes versus the costs of running a Molly device project.

DESIGN FOR MANUFACTURING & ASSEMBLY

DFMA is an engineering methodology that focuses on reducing time-to-market and total production costs by prioritizing both the ease of manufacture for the product's parts and the simplified assembly of those parts into the final product – all during the early design phases of the product lifecycle.

Modularizing Assembly and Testing Machines

While computer-aided manufacturing (CAM) concepts have been practiced in various industries for many years, there is still no universal guideline to applying these concepts in medical device development. In brief, CAM refers to the use of software or computer-controlled machinery to manufacture products. Automation for manufacturing, on the other hand, refers to the design and application of a system that enables automatic processes in the manufacturing stream. It could be said that CAM and automation for manufacturing concepts intertwine in ways that enable both the efficient and cost-effective mass production of a product. Also, both computer-aided and automated manufacturing practices rely on the application of DFMA in the product design process. In detail, this means that a device design must consider ease of manufacturability of each component (i.e., DFMA), which would then be supported by production infrastructure.

As has been discussed, these concepts are not new for various industries. However, there are no published standard principles of their application in autoinjector production for combination product projects. Interestingly, a PubMed search using a combination of the keywords "design for manufacturing", "medical device", and "autoinjector" yields no specific or highly relevant results. On the other hand, a PubMed search using a combination of the keywords "modular machine", "medical device", and "autoinjector" yields some relevant materials. This suggests that device companies are tasked with leading and innovating effective means of carrying out such complex manufacturing processes in the field of medtech. For device projects based on the Molly technology, modularization is applied not only to the device design but also to the manufacturing infrastructure that support it. SHL Medical automation experts Chung and Fluetsch (2019) presented an evidence-based practice of the modularization of assembly and testing machines for medical devices – autoinjectors in particular. Chung and Fluetsch further explained SHL Medical's recent take on the modularization testing machines in a 2021 publication – all of which are detailed here.

MODULARIZATION ACROSS MOLLY'S INFRASTRUCTURE

Modularity has been integrated not only in the Molly device design but also in the infrastructure that supports it. SHL's assembly and testing machines feature parts that are customizable to address the specific requirements of each Molly device project.

In response to the growing need for syringe- and cartridge-based injection devices, in 2018, SHL conceptualized and developed its first highly flexible and fully automatic testing machine (FATM). The FATM is flexible in allowing for mix-and-match testing options to accommodate different types of injection devices. From past machines that were custom-built for single device projects, the development of early versions of SHL's FATM signaled its move to create a more flexible and automated suite of testing machines built upon modular platforms. The current version of the modular machine can be seen in Figure 10.

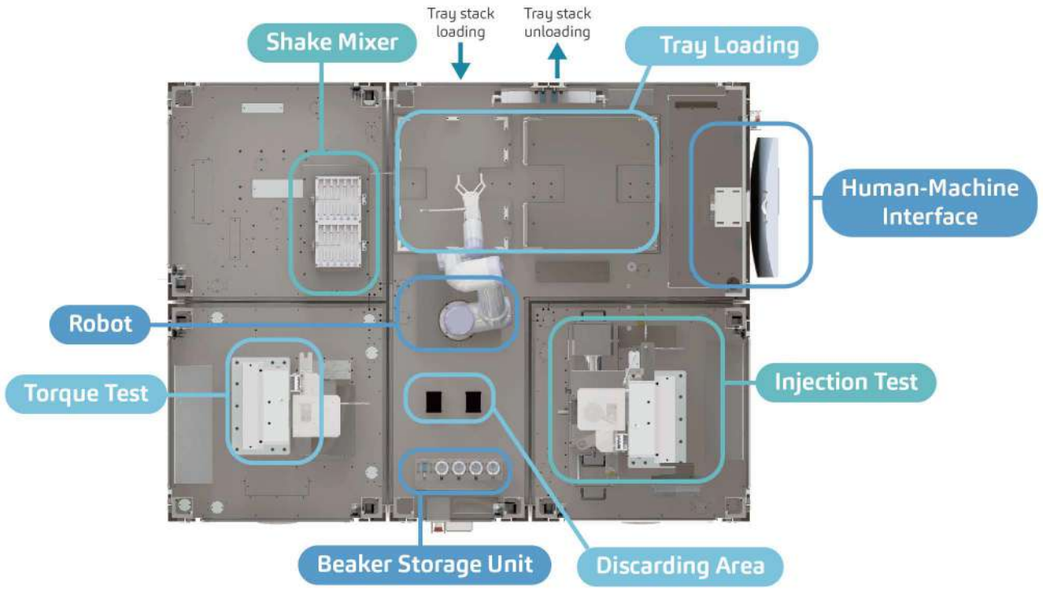


Figure 10: Top-view of SHL Medical's FATM with customizable stations that can accommodate not only syringe-based but also cartridge-based autoinjector testing.

In detail, the modular FATM features interchangeable tools and fixtures for increased device compatibility, as well as a modular platform base that can be arranged and expanded to accommodate various test stations. The machine is also integrated with a software program that enables the customization of test sequences. For a two-step autoinjector like Molly, such a modular testing machine can fulfill its testing needs, which include cap removal force, injection activation force, and injection test. More so, the accompanying software can be configured to accommodate the intricacies of the test sequences.

Similarly, the concept of modular technologies is applied not only to SHL Medical's testing infrastructure, but also to its assembly machines. Given that a combination product has manufacturing requirements conformant to usability studies, clinical trials, pilot commercialization, and sample requests from various stakeholders such as regulatory bodies, flexible assembly machines that address the interplay of these requirements are critical. Figure 11 outlines the depth and breadth of assembly and testing machines under SHL Medical to support the production scalability of autoinjector projects throughout their lifecycle.

Figure 11: An overview of SHL Medical's modular assembly and testing machines that support varying requirements of Molly device projects.

In the context of autoinjector development, the benefits here are compounded when both the device components and its assembly and testing infrastructure are built upon modular platform technologies. This complementation ensures that customizations in the device design can be assembled and tested through modular machines that feature interchangeable tools and stations corresponding to the device's characteristics.

SHL MEDICAL'S QUICK-TO-MARKET™ SERVICES

SHL's final assembly, labeling, and packaging solutions are parts of its Quick-To-Market™ services. In 2016, the service model led a migraine device project – featuring the Molly technology – from device development to clinical delivery in less than nine months.

Transforming the Molly Device to Molly-Based Combination Products: Final Assembly, Labeling, and Packaging Solutions

As mentioned, a key highlight of SHL's process development model is the integration of processes that have an impact not only on SHL but also on its pharma partners in combination product development. In a 2021 publication, SHL Medical detailed its integrative process development through to final assembly model:

1. Developing and performing all the device and syringe assembly (herein referred to as final assembly), labeling, and packaging processes for its customer projects
2. Building the customer's equipment needs in final assembly as well as guiding the final assembly process

While SHL can build the final assembly equipment for its pharma partners in both scenarios, the key point here is that there is flexibility in the production strategy that its pharma partners in both scenarios, can undertake. In the case of the former, SHL's final assembly experts synch with project teams to ensure successful design transfer and execution of the final assembly of the autoinjector with the primary container. This ensures the synchronization of deliverables during various phases of the project's lifecycle, where SHL ensures a successful final assembly process for the pharma partner through an established suite of contract manufacturing solutions (CMO). Further, these CMO solutions include device labeling and packaging capabilities through automatic labeling and packaging machines that feature serialization capabilities compliant with the regulatory requirements.

In the case of final assembly equipment commissioning for its pharma partners, SHL has the capacity to develop the client's device and the required final assembly equipment in parallel. This means that in the initial stage of device development, SHL's in-house process development engineers collaborate closely with the equipment engineers to provide guidance on the assembly process and acceptance testing, ensuring that the final assembly process effectively aligns with the specifications of the device. Prior to releasing the autoinjector sub-assemblies to its customers, SHL provides the design verification master report – a technical documentation comprising a suite of test methods, protocols, and reports detailing the particular device.[14, 15, 16, 17]

The Interplay of the Molly Modular Platform, Modularized Infrastructure, and SHL's Streamlined Process Development

Since its launch in 2010, Molly has supported the development and regulatory approval of 14 molecular entities found in 17 combination products covering a range of disease areas. In the course of these market launches and successes, the underlying technology has been proven and optimized over the years, in turn giving rise to the new generation of Molly that we know today.

No.	Approval Year	Device	Indication
1	2016		Autoimmune and Inflammatory Diseases
2	2016		Migraine
3	2016		Inflammatory Diseases
4	2017		Systemic Lupus Erythematosus
5	2018		Autoimmune and Inflammatory Diseases
6	2019		Autoimmune and Inflammatory Diseases

No.	Approval Year	Device	Indication
7	2019		Hypoglycemia
8	2019		Autoimmune and Inflammatory Diseases
9	2019		Hyperlipidemia
10	2019		Hyperlipidemia
11	2020		Atopic Disorders
12	2020		Atopic Disorders
13	2020		Autoimmune and Inflammatory Diseases
14	2020		Type 2 Diabetes
15	2021		Severe Hypoglycemia
16	2021		Autoimmune and Inflammatory Diseases
17	2021		Weight Management

Table 1: Combination products built with the Molly autoinjector technology that have gained regulatory approval and have been commercialized over the years. ***Brand names have been redacted and the list of disease indications is non-exhaustive.***

Looking at previously commercialized Molly device projects shows the competitive advantage of the current second-generation Molly, which is a modular platform. A bidirectional comparison of each commercialized device highlights the device technology's previously acquired but now inherent property that is flexibility in industrial design.

In Figure 12, the industrial design of all devices shown highlights the stark differences in design and flexibility afforded by a modular platform technology. This difference could further be translated into the requirements addressed in terms of the drug, patients' disease state, and user group handling needs, to name but a few. In addition, the Molly devices (no. 11-12) indicated in the figure as being commercialized in 2020 highlights how Molly can support lifecycle management, wherein the prefilled syringe and complex biologic has been co-developed in two device versions for varying dosing needs. It is interesting to note that these device projects were initiated within timelines independent of each other, highlighting the robustness of the Molly platform over time. Such a modular platform allows for bespoke offerings to every customer, which at the same time is supported by a design and manufacturing model that can be scaled according to the purpose and demands of production. Finally, the idea of bespoke device projects based on the Molly modular platform technology is further substantiated through a non-exhaustive but multi-source survey and comparison of commercially available platform-based autoinjectors.[18, 19]

It could be said that alongside these, experience with Molly projects translates into the parallel maturity of infrastructures that support the design and development ecosystem of such device projects. With a device technology built upon standard modules and mature infrastructures, Molly supports customized solutions according to individual drug, pharma, and patient requirements.

SHL Medical leverages the wealth of resources within the organization, and these come in the form of platform data, subject matter experts in the process development stream, as well as historical data that can be pulled from a myriad of past device projects that have commonalities in various elements.

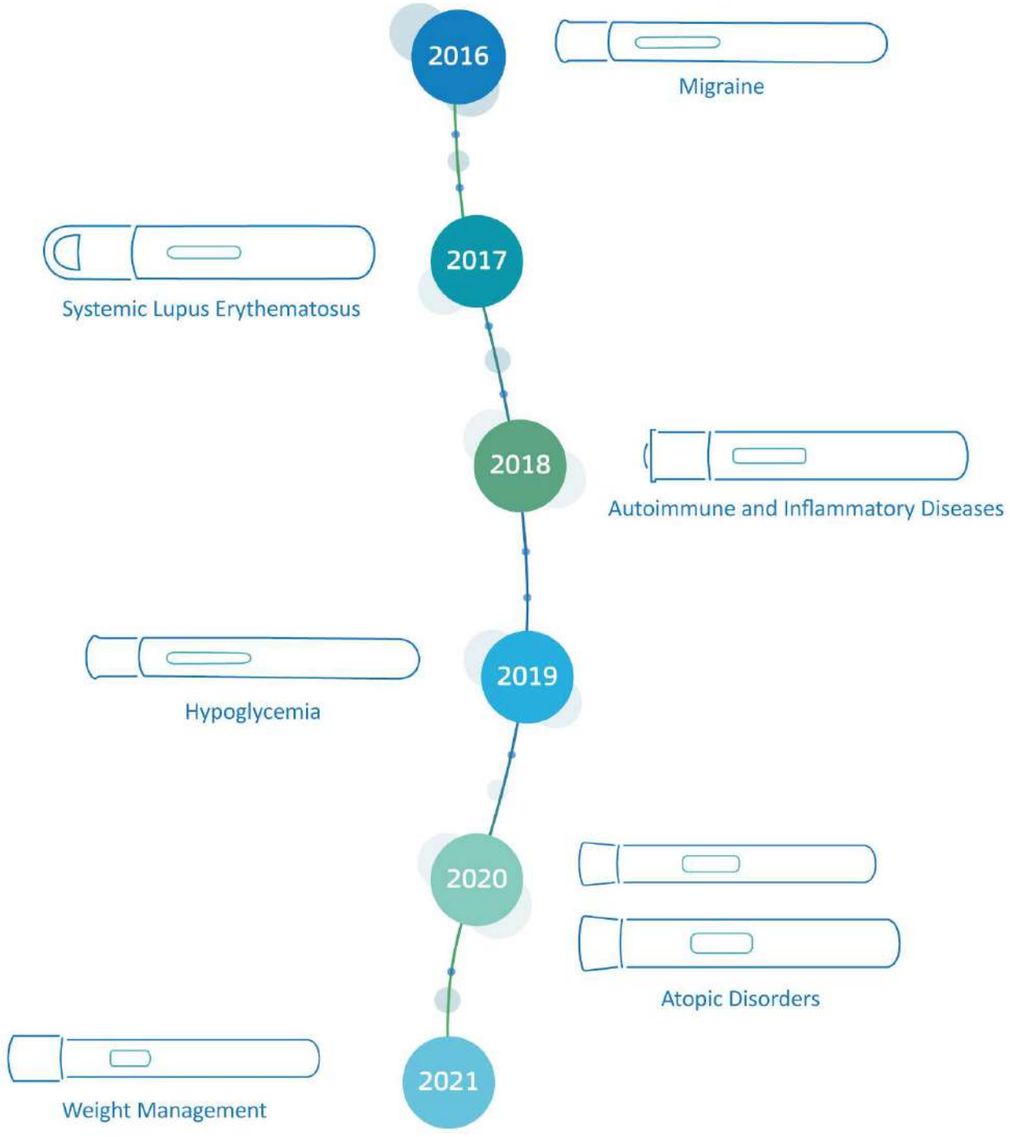
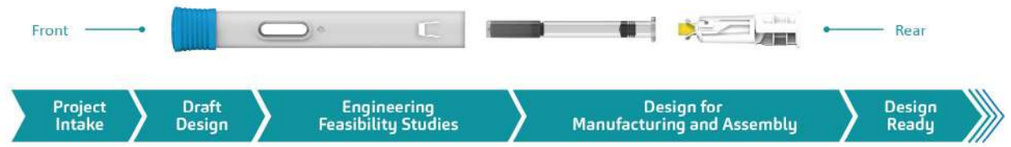


Figure 12: Commercialized projects based on the constantly developing Molly modular platform technology. Molly has been commercialized with a number of drugs in several markets around the world, and is one of the world's first high-volume autoinjectors to be commercialized.

The modular platform technology that enables the Molly device is the result of years of testing the platform parts and sub-assemblies as well as iterating designs to ensure a robust device offering. This has allowed SHL to develop a platform technology that allows for customizations in the front and rear sub-assemblies of the autoinjector, supporting an autoinjector device that addresses the requirements of the primary container, industrial design, as well as the usability needs of the end user.

Modular platform technology enabling customizable front and rear sub-assemblies



Production Specifications

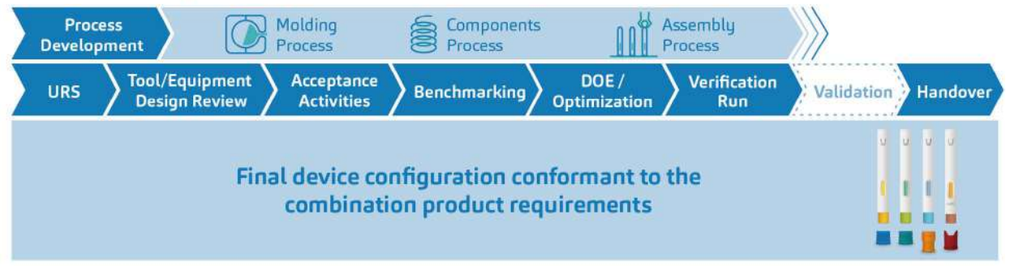


Figure 13: An outline of the interplay between the modular platform technology that exists in the Molly device offering, along with its streamlined process development strategy, which together allow for device configurations that are conformant to the highly specific requirements of any combination product. *Device renderings only, not representative of final device offering.*

03

ENSURING QUALITY & FACILITATING REGULATORY SUBMISSIONS WITH MOLLY PROJECTS

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Molly®

Modular Platform Technology

GOVERNING REGULATORY BODIES & STANDARDS ORGANIZATIONS

In the development of autoinjectors for combination products, the relevant regulatory frameworks and quality standards organizations include the US FDA, EU Medical Device Regulation, International Organization for Standardization, and International Electrotechnical Commission.

Introduction and Objectives

International regulatory frameworks and quality standards are some of the drivers in the design, development, innovation, and market launch of combination products. All drugs and drug delivery systems that reach end users must first pass science-based control mechanisms instituted by international regulatory agencies. Thus, the speed at which combination products under development can be introduced to the market is contingent on the fulfillment of required regulations. Consequently, the rate at which these combination products get approved by regulatory agencies depends on experience with fulfilling the requirements with effective regulatory submissions.

In principle, the success of a combination product launch is contingent on the regulatory approval of the drug-device for each region where it will be marketed. To initiate a regulatory review, a combination product's marketing application will need to follow a stringent set of requirements. A critical element in the submission process is the expert input from knowledgeable and experienced key resource individuals. Collectively, a well-informed and thought-through regulatory strategy will define the success of a combination product project's regulatory submissions.

SHL Medical's experience with developing combination product projects under the Molly technology, which was launched in 2010, brings it familiarity with applicable device regulations. This product lifecycle management experience, combined with quality management systems that comply with international standards, helps facilitate regulatory submission success for current and future Molly autoinjector projects.

Background

Supporting Regulatory Activities through SHL's Regulatory Centers of Excellence

At SHL Medical, the objectives of its global Regulatory Affairs (RA) team encompass the entire lifecycle management of a product. Working in a cross-functional team structure across three continents, SHL's global RA team facilitates the regulatory activities of each customer project through RA leads situated across its international sites. This working model ensures that customer projects are assigned experts that have experience in helping customers to secure regulatory submissions and eventual approvals in accordance with the requirements of the applicable regulatory bodies within the designated region. Beyond these global and regional competencies, fungible roles and skills are actively being developed within the organization.

REGULATORY CENTERS OF EXCELLENCE MODEL

The Centers of Excellence model, as contextually defined at SHL Medical, refers to its global and regional work approach in supporting customers to secure regulatory submissions in accordance with the requirements of the applicable regulatory bodies within the designated region.

To ensure the regulatory compliance of operations, SHL has established a regulatory intelligence process and regularly performs gap analyses and applicability assessments to identify key areas in all processes undertaken within the organization that need to align with the applicable regulatory requirements.

Aside from regulatory compliance, continuous process improvement is also part of the RA team's regular operations. This practice would result in activities such as template establishment for device project-related submission dossiers, as well as having an applicability matrix for relevant international regulatory standards. For customers, this ultimately translates into speeding up marketing lead time.

Figure 14: SHL Medical's cross-functional regulatory affairs structure built upon the Centers of Excellence model.

CURRENT GOOD MANUFACTURING PRACTICE

As defined by the US FDA, Current Good Manufacturing Practice refers to systems that ensure the proper design, monitoring, and control of manufacturing processes and facilities. Adherence to the regulations ensures the quality of products by requiring adequately controlled manufacturing operations.

Safeguarding Quality Standards through an Established Quality Management Systems

The challenge to establish a quality system from a global perspective – satisfying all relevant US, EU, and Asian regulations, as well as ISO requirements – is a pressing concern for combination product developers. Whereas drug development is focused on drug discovery, pre-clinical and clinical tests, as well as mass production, medical device development is focused on enabling safe and effective delivery to its intended users and patients. At present, the rising trend in biologics administrable through subcutaneous means opens new but intertwined quality and regulatory pathways for combination products, where devices like autoinjectors are seen as an integral component of the combination product that ease drug delivery. Accordingly, this translates to combination product projects wherein pharma partners are tasked with creating design controls historically absent in the quality systems they established for drugs or biologics Current Good Manufacturing Practice (CGMP).

As with every device development under SHL Medical, projects with pharma partners under the Molly autoinjector technology are supported with an established quality agreement. This agreement is in accordance with generally accepted principles and rules encompassing the manufacture and quality control of such devices. Full emphasis is given to the fact that this quality agreement specifies the governance and clear cooperation structure between SHL and the pharma partner for design control. Aside from quality agreements, development and supply agreements are also put in place to ensure a well-defined device project. A critical highlight of these agreements is that their composite encompasses the technical, safety, and quality aspects of all the components and sub-assemblies of the autoinjector device.

COMMERCIAL SUCCESSES

Since the launch of the Molly autoinjector technology, a total of 17 combination products have been commercialized covering 25 indications for various systemic disease states. These Molly-based self-injection devices have so far been made available in more than 30 countries across the world.

Discussion and Analysis

Experience with Combination Product Projects Under the Molly Technology Facilitates Regulatory Submissions

Looking at past projects from a regulatory perspective, the well-established RA team and quality systems that support Molly projects have allowed for meeting each pharma partner's timelines for regulatory submissions. These projects benefited from standardized product development process documentations and relevant design controls that capture the core of the Molly autoinjector technology. As of 2021, a total of 17 combination products had been launched as part of the Molly autoinjector family. In detail, the utilization of the Molly technology has been proven successful in obtaining regulatory approvals and eventual product launches in disease areas such as rheumatoid arthritis, diabetes, and even atopic dermatitis. The figure below is an intensity map of Molly commercial launches worldwide visualizing the sum of device units per country.

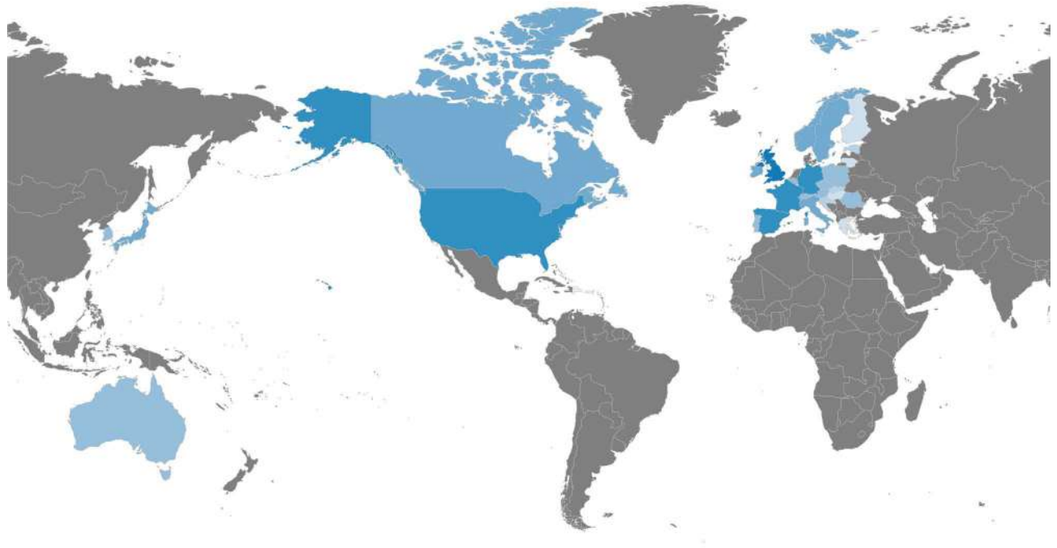

Figure 15: Intensity map of Molly commercial launches showing the relative sum of device units per country.

QUALITY AND REGULATORY SYSTEMS AT SHL MEDICAL

SHL Medical maintains a tight integration of its quality and regulatory operations in supporting the design, development, and production of all autoinjector technologies that it co-develops with its pharmaceutical partners. Contextually, this means that quality assurance and RA systems within the organization are mutually inclusive.

While regulatory standards and regulations have constantly been evolving over the years, the Molly autoinjector device has proven to be an adaptive technology. The European Medicines Agency's 2021 revised regulations on medical devices (Regulation EU 2017/745) state that:[20]

For medical devices that form an integral product with a medicinal product (Regulation (EU) 2017/745, second subparagraph of Article 1(8) and 1(9)), new requirements to provide an EU certificate or an opinion from a notified body designated under Regulation (EU) 2017/7451 for the type of device in question is applicable in certain circumstances (Art. 117).

Case in point, an SHL autoinjector device commercialized in 2021 went through the EU Medical Device Regulation NB opinion with a positive outcome with one of SHL's customers. The self-injection device features SHL's Molly modular platform technology with a GLP-1 receptor agonist. Notably, the US approval in 2021 of this new subcutaneous combination product, now indicated for an underlying pathophysiology other than diabetes, was the first such approval of a new drug treatment for chronic weight management since 2014.[21]

Established Quality Management Systems Support Lifecycle Management of Molly Projects

From a quality perspective, SHL Medical's QMS complies with relevant regulations and provides each project with informed and risk-based decisions in establishing CGMP. Ultimately, these quality standards support the efficient and effective development, manufacture, regulatory submission and evaluation, as well as commercialization of each project based on the Molly technology.

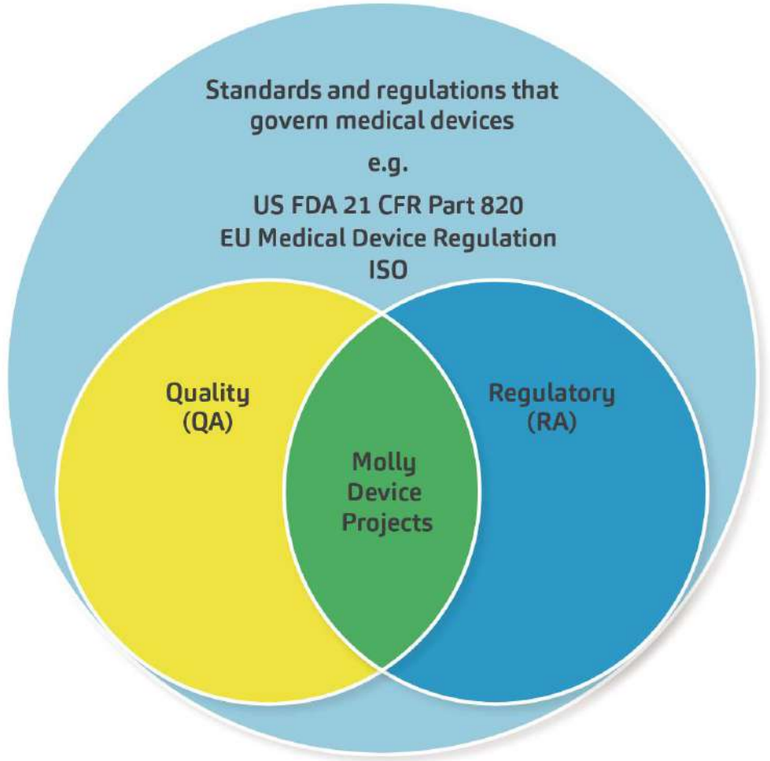

Figure 16: A Venn diagram of the propositions relating the Molly technology with SHL Medical's quality assurance and RA systems, as well as the standards and regulations landscape governing the whole medical device industry. The yellow and blue circles refer to SHL Medical's quality and regulatory systems, the union U of which supports all Molly device projects within the organization. Note that the general standards and regulations listed in the biggest circle is non-exhaustive.

04

SYNTHESES & CONCLUSIONS

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Modular
Platform Technology

AUTOINJECTOR PLATFORMS

Autoinjector platforms in the medical device industry are generally characterized by their tendency to be developed according to predefined parameters and communal units.

Understanding SHL Medical's Modular Approach to the Expanding Molly Ecosystem

The Molly modular platform device technology offers a range of advantages. From a general medical science perspective, the device technology's 10-year record has so far yielded 17 combination products (see Chapter 2, Table 1) addressing various disease areas. It is worth noting that these disease areas cover fields like rheumatology, endocrinology, immunology, gastroenterology, and dermatology, exhibiting the depth and breadth of combination product approvals under the device technology. When it comes to the structural diversity of the biopharmaceuticals that have been put together with the device, the autoinjector technology supports 14 molecular entities covering at least 25 clinical indications across the aforementioned disease areas. These have all resulted in the availability of the Molly autoinjector as a combination product commercialized in more than 30 countries (see Chapter 3 Figure 15).

The data gathered and presented in the paper indicates that the Molly modular platform device technology functions beyond what is defined as a conventional platform. In an article published by SHL Medical in 2020, an extensive data search and analysis on the definition of platform technologies led to the following qualitative observations about such autoinjector devices:[22]

1. Fast time to develop based on a preconfigured device design
2. Availability of common toolsets for device parts, supporting reduced initial costs
3. Preset industrial design vetted for various user-group scenarios.

Clearly, platform technologies are centered on predefined parameters and communal units. Furthermore, this paper also demonstrates how the Molly device technology leverages the advantages of preconfigured elements through the use of modularity. Figure 12 as well as Table 1 of Chapter 2 exemplify the heterogeneity in the industrial design of autoinjector products that rose from the Molly modular platform technology.

DIGITAL HEALTH AND CONNECTED THERAPEUTICS AT SHL MEDICAL

Digital health is continuously being combined with SHL Medical's drug delivery technologies through the Connected Therapeutics Innovation Partnership (CTx). The CTx Innovation Partnership is a co-creation process that leverages SHL's technological capabilities with pharma's clinical innovations.

This heterogeneity has been made possible by modularity, an aspect of the device technology that has been extensively covered in Chapter 2. Here, modularity can be seen in the automated assembly and testing machines that support the device technology, as well as the customizable configurations of the front and rear sub-assemblies of the device. It should be noted that heterogeneity is viewed here in a positive sense, as it offers competitive advantages to autoinjector products in the market. It is also understood that the expanding ecosystem of the Molly platform includes modules that represent digital health and sustainability.[23]

Digital Health and Sustainability at SHL Medical

In a 2021 research study published in the *Journal of Medical Internet Research*, SHL Medical conducted an analysis to assess the digital health maturity of the US biopharmaceutical industry. The study utilized a five-point scale to assess biopharmaceutical companies across four digital health segments, namely clinical research and drug discovery, lifecycle management, product commercialization, as well as beyond the molecule solutions. The study demonstrates the differences in biopharma maturation and offers a view on the necessity for pharma to design a pathway to embed digital health in its solutions to realize the full potential of biologics, all the while driving innovation in autoinjectable devices.[24]

On the other hand, it could be said that the paper denotes SHL Medical's active pursuit of integrating digital health in its portfolio. One way in which SHL implements its strategy for combining drug delivery technologies, such as the Molly autoinjector, with digital health is through the Connected Therapeutics (CTx) Innovation Partnership. The CTx Innovation Partnership is a co-creation process that leverages SHL's technological capabilities with pharma's clinical innovations. The CTx scheme, visualized in the figure below, is aimed at creating the baseline for a tailored, innovative digital health ecosystem built on connectivity and meaningful data at scale.

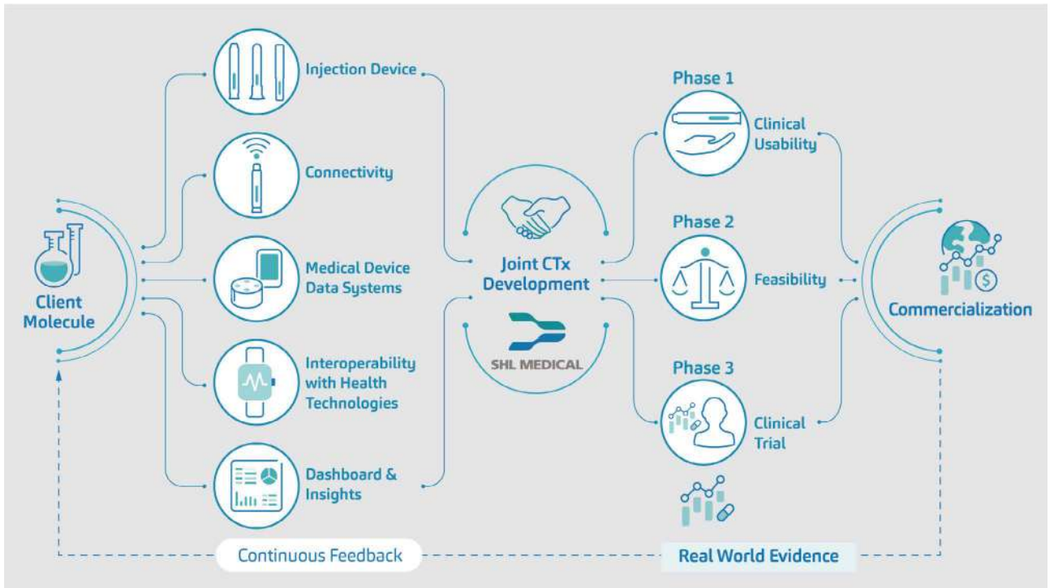

Figure 17: SHL Medical's Connected Therapeutics Innovation Partnership.

ENVIRONMENTAL, SOCIAL & GOVERNANCE FRAMEWORK

Environmental, social, and governance (ESG) is a broad concept used for evaluating an organization's collective performance regarding social and environmental factors. ESG consists of three central elements in measuring the sustainability and impact of a company's operations.[27]

SHL Medical's Environmental Social Governance Strategy reflects the organization's proactive efforts in ensuring an inherently sustainable Molly autoinjector. Given the many discussions on carbon footprints and their detrimental effects on the general health of the population and the environment, SHL has been actively pursuing initiatives in sustainable product design and development principles across Molly device lifecycles. SHL's sustainability strategy has three key pillars (the three Ps), as outlined in the figure below:[25]

Figure 18: A diagram depicting SHL's sustainability commitments, namely in the three key areas of Product, People, and Planet, referring to sustainable designs, a sustainable society, and a sustainable environment, respectively.

MODULARITY BUILT UPON A PLATFORM

The Molly modular autoinjector platform technology takes a non-conventional approach to platform design by integrating modules into its ecosystem. These modules refer to the Molly device design and core technology, manufacturing infrastructures, and add-on features that respond to digital health and sustainability imperatives, as well as the ever-changing market landscape.

SHL's sustainability initiatives relevant to the Molly technology ecosystem include:

1. Sustainable product principles that cover the device's design, development, and production, with the aim of introducing alternative materials into its design and processes.
2. Energy-efficient features in the manufacturing site as well as streamlined material-handling processes that reduce water usage, production waste, and CO_2 emissions.
3. Investments in fully electric molding machines that have already resulted in significant energy savings as well as a cleaner and more efficient production.
4. Sustainable packaging wherein trays used for internal/local transportation are reusable. Trays made from 100% recycled plastics are planned to be introduced in 2025.
5. Supply chain activities that utilize reusable transport materials, active analyses of how to reduce SHL's environmental footprint through updates to palletization schemes and intermediate and shipping storage configurations.
6. Establishing a well-proven modular component and equipment strategy, allowing SHL to assemble and test different variations of Molly devices with interchangeable fixtures. By reusing much of the same machinery for different projects, emissions from producing and operating individual machinery are significantly reduced.

Given these constant modular expansions to the Molly ecosystem, the device technology has certainly risen beyond the confines of a platform-based autoinjector. With an ever-changing healthcare landscape that is dependent on pharmaceutical companies and their biologics pipeline, the need for convenience in chronic disease treatment, as well as the development of patient-centric solutions in enabling patients' independence, device technologies that redefine conventionality in self-injection will be increasingly critical to driving future growth.

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SHL Medical is a world-leading solutions provider in the design, development, and manufacturing of advanced delivery devices, such as autoinjectors and pen injectors. We also offer advanced wearable injection systems, as well as final assembly, labeling, and packaging solutions for global pharmaceutical and biotech companies.

With locations in Switzerland, Taiwan, Sweden, and the US, our experienced designers and engineers develop product enhancements and breakthrough drug delivery solutions for pharma and biotech clients globally. Significant investments in R&D have enhanced our broad pipeline of next-generation drug delivery systems that support ongoing innovations in drug development and digital healthcare. This includes advanced reusable and disposable injectors that can accommodate high-volume and high-viscosity formulations and can be enhanced through digital implementations.

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