White Paper

AUTO INJECTORS FROM PLANNING TO LAUNCH

Preparing for the overall development process

SHL GROUP

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Version 1.2

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1 INTRODUCTION

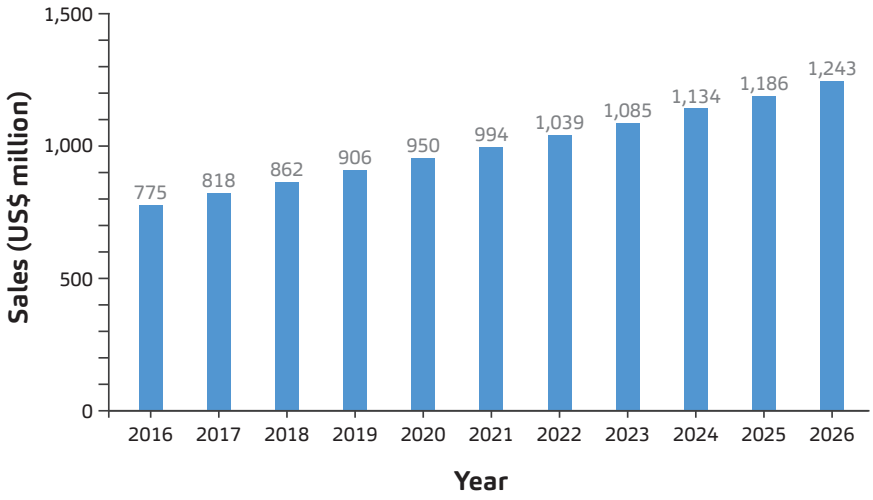
1.1 OVERVIEW

- The market for auto injectors is estimated to reach US$1,243 million by 2026.
- Over 30% of all new product submissions to the FDA are combination products with auto injectors being one of the fastest emerging solutions.

Looking at the rising trend towards self-administration therapies, injectable drug delivery devices, such as pen injectors, auto injectors and needle free injectors, have continued to show significant growth in the international market.

In 2016, the auto injectors market was estimated to be worth approximately US$775 million with an annual output of 69 million units. It is estimated that the market will continue to grow at an annual rate of 7.6%, and will reach US$950 million in 2020 and US$1,243 million in 2026 (Roots Analysis, 2016).

Figure 1: Overall Auto Injectors Market Forecast, 2016-2026



(Source: Roots Analysis)

Driven by the industry demands, biopharmaceutical companies have since introduced a large range of solutions for delivery of injectable drugs and continue to push for improvements in every aspect. In fact, industry analysts have estimated that over 30% of all new product submissions to the FDA are combination products (Richter, 2011). Of these, the auto injector is one of the fastest emerging drug delivery solutions that enhance patient experience and compliance by allowing them to safely self-administer medications at home. Aside from patient benefits, the resulting reduced number of clinic visits can help lower the costs for health

authorities by removing burden on nurses/Healthcare Providers (HCPs) to deliver face to face treatments. The various ergonomic designs and safety mechanisms built into the auto injector also help address patient dexterity concerns and minimize the possibility of needle-stick injuries for HCPs assisting with the delivery.

The auto injector is now often considered by many biopharmaceutical companies to be a suitable device to commercially launch their therapeutic drugs. To do so successfully requires detailed planning, combination product knowledge, regulatory awareness and close collaboration with a carefully chosen device manufacturer. Unfortunately, biopharmaceutical and device companies have different product life cycles and development processes, which can lead to process gaps that are crucial to the overall project and can ultimately influence the product's speed to market. It is, therefore, imperative that the biopharmaceutical company has a thorough understanding of all related processes; when and where to involve the device manufacturer; how to meet the corresponding regulatory demands for combination products; what core competencies to seek for; and more.

- Combination products require close collaboration between biopharmaceutical companies and device manufacturers who have different product life cycles.
- An auto injector consists of a PFS or cartridge and a mechanical mechanism inside a device to deliver the drug.

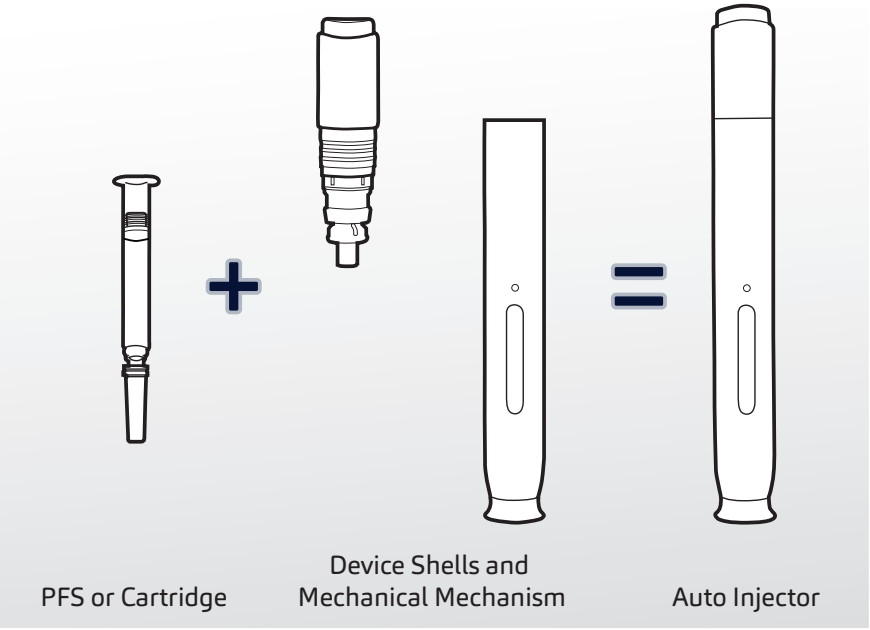
This white paper focuses on assisting biopharmaceutical companies in taking a closer look at the development process of an auto injector project from planning to launch and at the best practices on how to prepare for and address potential challenges along the way.

1.2 A COMBINATION PRODUCT IS A JOINT EFFORT

An auto injector consists of a prefilled syringe (PFS) or cartridge inside a device with enough mechanical force to fully inject the desired drug within the specified delivery requirements. Both of these are regulated components and together define the auto injector as a combination product.

For patients, some beneficial features of the auto injector include reduced dosage errors, integrated needle safety and a mechanical design that can overcome patient concerns such as needle phobia and dexterity challenges. As a healthcare provider, aside from simpler and more streamlined preparations, the auto injector also offers a safer alternative that can help prevent against needle stick injuries, a major concern that on average causes between 600,000 to 1 million injuries in the US (US Medical Instruments, Inc., 2006) and a global injury rate affecting up to 3.5 million individuals (Prüss-Ustün, Rapiti, & Hutin, 2005). The severity of the injuries can lead to serious infections through exposure to blood-borne viruses (BBV) such as Hepatitis B (HBV), Hepatitis C (HBC) and Human immunodeficiency virus (HIV).

Figure 2: The Auto Injector, a Combination Product



- Auto injectors can reduce dosage error, integrate needle safety and address needle phobia and dexterity challenges.
- Offering biologics in an auto injector can help maintain market differentiation and protect product with additional IP.
- The desired prefilled syringe (or cartridge) inside the auto injector will impact the overall device design.

Aside from the patient and administrator oriented benefits of the auto injector, the range of mechanical designs the device offers also makes it a favorable consideration for biopharmaceutical companies. While approved biologics can stay on the market decades at a time, once they are off-patent and face loss of exclusivity, the original innovators need to take protective measures by introducing more market competitiveness to the overall product. Offering the biologic in an auto injector allows the biopharmaceutical companies to provide consumers with various administration benefits and, at the same time, maintain market differentiation with a layer of IP protection from the device.

With the advantageous business and consumer factors the auto injector presents, it has in recent years become an industry standard and user favorite for self-administered injectable treatment for patients with chronic diseases, such as multiple sclerosis and rheumatoid arthritis. Other applications include treatments for Hepatitis C, anemia and anaphylactic shock.

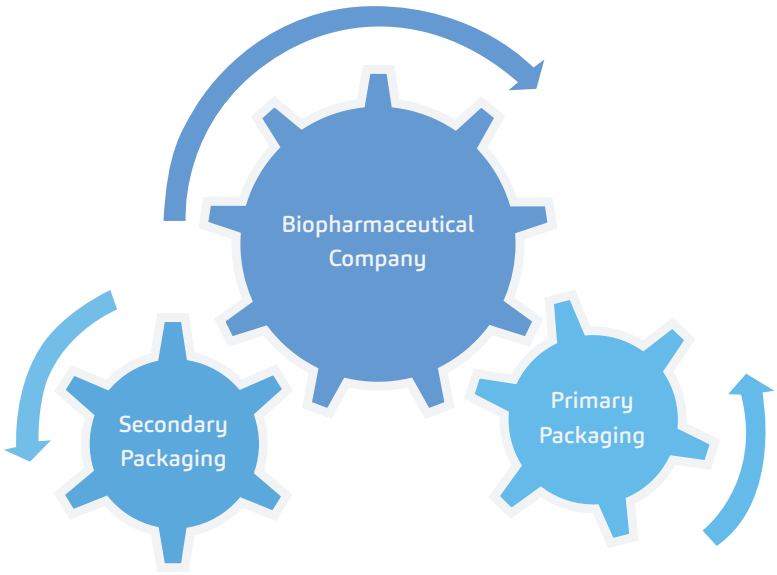
The design of an auto injector is impacted by the PFS (or cartridge) inside and, when required, is specifically designed around it. Fortunately, the PFS has already been widely used and many biopharmaceutical companies are familiar with the

associated stability and compatibility concerns such as extractable and leachable implications on the contained biologics. However, with researching and developing drug formulations the traditional focus for biopharmaceutical companies, integrating the PFS into an auto injector brings new challenges in areas of unfamiliar expertise such as mechanical design and manufacturing and will involve immense education and awareness as well as a carefully chosen partnership. New items that will require such attention may range from the initial user-centric design of the device to the assembly of the components, associated regulatory matters and more. Assuming the biopharmaceutical company has specified the type of PFS (e.g. standard 1mL long) to use in the auto injector and an associated primary packaging vendor, considerations of the above secondary packaging matters and choosing a device partner become another key piece for the success of a combination product.

Primary Packaging
This refers to the container that is in direct contact with the drug, e.g. prefilled syringes and cartridges.

Secondary Packaging
This refers to the device that contains the primary container.

Figure 3: Relationship between Biopharmaceutical Company and Packaging Partners



A biopharmaceutical company will need to work closely with both their Primary and Secondary Packaging partners to ensure the project's success.

- The biopharmaceutical company will need to work closely with both Primary and Secondary packaging partners to ensure success of an auto injector product.

With so many interrelated variables, a biopharmaceutical company that wishes to venture into the auto injector market will need to understand what core competencies to look for in a device partner and educate themselves about the overall auto injector development process and pitfalls to avoid as early as the planning stage. Once a chosen device manufacturer is engaged, close and frequent communication will be essential during all phases from planning to launch to

ensure potential bottlenecks are either avoided or addressed in a timely fashion. The extent of the joint effort between the biopharmaceutical and device companies can determine the overall success of the auto injector project.

1.3 FROM PLANNING TO LAUNCH

Introducing a competitive product that meets user needs and can be launched within the desired time to market is the ideal goal for any biopharmaceutical company. Working towards this goal becomes a reality as the biopharmaceutical and device companies come together to design and coordinate an auto injector project.

Figure 4: From Planning to Launch

The 3 main stages of an auto injector project: Planning, Development and Launch should and will influence each other.

The chart is broken down into three main stages: Planning, Development and Launch, and will be discussed in more detail in the subsequent sections of this paper. However, as with any product that involves end-user experience, linearity is almost never an option as post-launch product responses should circulate back

to directly influence future development of similar projects and be factored into future design considerations (see Figure 4). Understanding and applying this concept is part of a series of best practices that will also be discussed later in this paper and can add value to similar auto injector projects the biopharmaceutical company takes on in the future. After all, a product that stops being better stops being good.

2 PLANNING

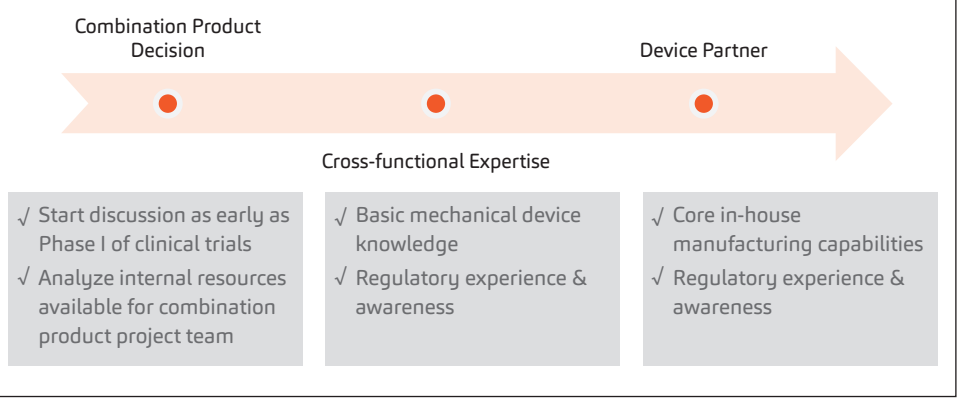
2.1 GENERAL SCOPE

- Auto injectors may be the preferred solution to address therapies with specific requirements, such as self-administering the injection of a viscous drug.
- Biopharmaceutical companies should initiate discussions about delivery plaforms as early as Phase I of clinical trials.
- Evaluate resources available internally and prepare accordingly.

With a majority of biologics recently introduced or in development made from complex chemical compounds, traditional oral intake methods may no longer be an option as the digestive system can cause unwanted chemical reactions Looking to other alternatives, delivery methods ranging from traditional vials, PFS, safety syringes and auto injector may all be considered. For biopharmaceutical companies that plan on introducing an injectable drug with special properties (such as high viscosity) and/or delivery methods (such as self-administration), the auto injector may quickly become prevalent in the pool of preferences.

A biopharmaceutical company should initiate discussions both internally and with a potential device partner regarding final delivery platforms as early as Phase I of a drug's clinical trials. With delivery specifications such as dose-ranging likely studied at this stage, involving a device manufacturer early can help identify possible mechanical limitations for delivery specifications and allow more time for the device manufacturer to innovate around them. For example, highly viscous drugs will require a specially designed mechanical mechanism for delivery but the corresponding shear force may have unprecedented effects at a chemical level. Discussing such issues early can impact the development timeline to follow. At this point, the question of how well prepared the company is should also come to mind, including the range of internal resources accessible and traits to seek in the chosen device partner. This initial evaluation is crucial especially if one has little or no experience with combination products. A prepared team will be the first essential step in the right direction.

Figure 5: Planning Checkpoints



2.2 INTERNAL RESOURCES

The team assembled for leading an auto injector project should first evaluate if the following items are available internally:

2.2.1 Cross-functional Expertise

Sufficient cross-functional expertise ranging from empirical to regulatory and basic mechanical device knowledge is essential on the team in order to better prepare for the project:

BASIC MECHANICAL DEVICE KNOWLEDGE

A biopharmaceutical company may have abundant experience working with therapeutic drugs and even introducing them into a PFS, but may have none in integrating them into an auto injector. While finding a partner with the right expertise in this area is crucial, obtaining some basic mechanical device knowledge can help the team better prepare for the device-drug combination product. Various auto injectors already exist on the market and with some thorough research, the assembled project team can discover what aspects of the device's mechanical design should be attended to most and specified to accomplish the administration for the desired drug. Such standard specifications may include:

Button Activated
The injection is activated through a push of a button.

Shield Activated
The injection is activated through the front shield of the auto injector when pressing the device against the skin.

Table 1: Examples of Auto Injector Device Specifications

Specification	Example(s)
Delivered Dose	1.0mL
Viscosity Range	1-50cp depending on needle and injection time
Injection Time	Over period span of seconds
Injector Mechanism	Mechanical, electronic
Injection Depth	Intramuscular, subcutaneous
Primary Container	Prefilled syringe (PFS), standard or dual chamber cartridge
Activation Method	**Button activated, shield activated**
Feedback Mechanism	Audible, visual, tactile
Needle Protection	Rigid/rubber needle shield, passive needle cover
Usage	Single dose, multiple dose
Dosage Type	Fixed, variable
Needle Attachment	Pre-attached, manually attached
Needle Insertion/Removal	Automatic, manual

The above is only some of many possible specifications that will affect the mechanical design of the auto injector. More details and guidance will often be provided by the device company, which may design the auto injector to fit a range of injection specifications. Having a fundamental understanding of the device's mechanics beforehand allows for a more accurate and detailed initial requirement request to the device company. Clearly specifying the mechanical needs for the drug at the initial stage can also minimize time-consuming adjustments later and enhance communication, pushing the project forward more quickly and efficiently.

However, unless members of the team have had extensive experience with mechanical devices, there will still be a limit to the amount of knowledge that can be obtained during planning whether it's through studying or utilizing other consultative means. Taking apart an auto injector to analyze its mechanical makeup is possible and can prove to be useful, but comprehending fully the design intentions behind each component is altogether more difficult without an intimate knowledge of the device's design history and is better left for the device manufacturer to provide.

Other mechanical features of the auto injector such as safety features and activation method will also have a direct impact on end user experience, making it even more imperative to acknowledge and factor them in at an early stage.

REGULATORY EXPERIENCE

- Key regulations to be familiar with include cGMP, QSR for the US and MDD for EU.
- Joint regulatory planning by both the device and biopharmaceutical companies is vital to ensure regulatory submission timelines are met.
- Combination products such as the auto injector can require more than one type of regulatory submission.

As the drug and device companies come together to work on an auto injector, they will enter an unfamiliar territory where the combination of the pharmaceutical cGMP (current Good Manufacturing Practice) regulation and device Quality Systems Registrars (QSR) must be applied for the US market, requiring close communication between both parties. At least one member of the biopharmaceutical project team should be aware of all related regulations and establish a communication protocol with the device company early, so as to ensure submissions do not delay project timelines. Likewise, the partnered device company should have a team of regulatory experts with experience working with the FDA on combination product submissions as part of its core expertise.

While the purpose of the cGMP regulation and QSR is to ensure that quality standards and regulatory requirements are met, they are tailored to very different products, making them challenging to grasp at times. Fortunately, the FDA has published draft guidance on drug/device combination products, a document that should be studied by the regulatory team on both sides during the partnership. This guidance and further information can be found at the FDA website (http://www.fda.

gov/CombinationProducts). For the EU market, a solid understanding and implementation of the Medical Devices Directive (93/42/EEC) is crucial. Depending on the type of auto injector (i.e. disposable or reusable) the device may require a CE mark. Directly speaking to and seeking advice from the corresponding regulation agencies and describing the type of combination product to be developed can also be helpful.

Regulatory planning is critical to an auto injector, as submission deadlines can drive project timelines; thus, sufficient planning, preparation and awareness are critical. Combination products such as the auto injector can sometimes involve more than one type of regulatory submission in order to market and distribute the final product (i.e. for the drug and separately for the device). It thus becomes even more valuable to have cross-functional expertise on the project team, including members who have experience working with drug/device combination products (such as inhalers) or with similar drug delivery products such as PFS and safety syringes. Familiarity with relevant manufacturing processes may prove to be helpful, but a biopharmaceutical company that focuses on excelling in drug research may find it more practical to cooperate with a manufacturing device partner who has the technical expertise and familiarity with FDA-recognized standards required for testing of drug/device combination products.

Whether the final product is for the US and/or the EU markets, cooperation between the biopharmaceutical and device companies is critical for the required pre-approval inspections by regulatory authorities. A joint decision must be made on who will be responsible for the various compliance documents and where they will be stored.

2.3 IDENTIFY A KNOWLEDGEABLE AND EXPERIENCED PARTNER

With a prepared internal team now ready, the biopharmaceutical company can begin evaluating different device manufacturers as their potential secondary packaging partner.

2.3.1 What to look for in a Device Partner

In-house manufacturing capabilities, regulatory experiences, structured risk and management processes are just some of the vital traits an ideal device manufacturer partner should have to ensure the end product quality, regulatory compatibility and time to market.

While many device companies in the drug delivery industry have experience working with auto injector projects, only a few can provide the range of core competencies needed to successfully see the project through from planning to launch. The list below is a proposed guidance for the biopharmaceutical company to reference when seeking a partner.

- √ An established track record and solid pipeline of auto injector products/ projects that reflect extensive experience in designing for drug substances of different physiochemical properties and varying injection requirements.
- √ A team of regulatory experts dedicated to supporting and coordinating various regulatory aspects of the project. This team ideally would have experience with FDA regulations, European Medical Devices Directive, and other countries' requirements, depending on where the product will be marketed and distributed. This team should report directly to an executive to escalate urgent matters when needed. Possession of 510(k) clearance, CE Mark, etc. for device platforms is also preferred.
- √ Knowledgeable project management teams to orchestrate, provide support and document the whole project from initial discussion to development and production.
- √ Strict and proven manufacturing quality control systems in place during all production stages.
- √ Strong in-house manufacturing capabilities and experienced operating personnel to support frequent design changes during scale-up or any other development stages (further explored below).

IN-HOUSE MANUFACTURING CAPABILITIES

In-house manufacturing capabilities are vital when supporting design changes during scale-up or any other development stages. Some core capabilities to look for in a device partner include:

- Tooling
- Molding
- Assembly
- Automation
- Metrology
- CNC Machining

- Possessing key core capabilities in-house allows the device company to have full control and ensure quality as well as addressing changes in a timely manner.
- The regulatory team of the device company should be experienced with similar projects and familiar with related submissions.

Manufacturing an auto injector requires complex processes and machinery. By possessing these capabilities in-house, the device company will have full control of the development processes under one roof, ensuring quality and addressing any needed design changes in a timely manner while the auto injector is still being optimized to meet usage requirements. As an example, dimension precision of components is key to ensuring the auto injector's proper assembly. With molding and tooling done in-house, new injection molds can quickly be provided to support the often frequent adjustments to a component's dimension.

Offering an extensive range of core manufacturing capabilities indicates that the manufacturer has made significant investments to provide a business model that makes the most sense for the biopharmaceutical company, a trait signifying dedication to the project. Overall, a device company that can provide it will have better insight into the auto injector's development stages and anticipated product life cycle as well as solid knowledge base that can help better determine and manage project scopes.

REGULATORY AWARENESS

As important as being familiar with regulations such as the cGMP regulations, QSR and MDD, the device partner needs to have a strong awareness of how associated regulations may affect the overall timeline. Ideally, the available regulatory team from the device company should have experience with similar projects and related submissions, so as to provide insight and specialized considerations when working with the biopharmaceutical company on projecting timelines. Regulatory teams from both the device and biopharmaceutical companies will also need to communicate early and frequently to define the intended use, indication for use and targeted markets of the combination product as well as the corresponding regulatory pathway required to achieve final approval. Necessary documentation should also be available to meet the biopharmaceutical company's corresponding clinical trials and associated submission dates.

Working with a partner that already has 510(k) clearance on device platforms can also significantly expedite the overall submission process and is a desirable trait the biopharmaceutical company should seek in a device partner.

2.4 LONG-TERM IMPROVEMENT MEASURES

2.4.1 Systematic Documentation

- Establish an internal project knowledge bank early to reduce internal miscommunication and save significant time for similar projects in the future.
- Complaint handling programs should be established to handle post-market responses and reports shared readily with the device company.

On average, an auto injector project can take 2 to 5 years to complete. With this time span, it becomes essential to establish a systematic documentation process internally beyond Document History File (DHF) regulations. This process should build towards a comprehensive knowledge bank in areas such as choice of material, justifications for device design adjustments, handling study parameters, regulatory obstacles encountered, post-market feedback and more. The centralized knowledge bank can provide a reference for the rationale behind each key project decision and reduce miscommunication amongst the many team members that may get involved during a potentially long project time span. For similar projects in the future, new project members can save significant time by referring to these documents to better understand the overall scope of an auto injector project and to avoid any known issues documented early.

The implementation of such a system is subject to how each assembled team operates but should be ready as early as planning stages.

2.4.2 Post-market Performance Monitoring Measures

The auto injector, compared to the traditional drug administered in a hospital or clinic setting, is mainly distributed through retail pharmacy portals. This adds a layer of complexity as users are directly purchasing a mechanical device and, if not properly trained, can encounter struggles due to incorrect usage. Consequently, the product's market performance can quickly be affected if a thorough customer training and service program is not in place to support the post-launch.

Developing such a program requires involving the biopharmaceutical company's internal Sales/Marketing and Regulatory teams, sharing with them vital handling study results and device usage instructions to allow a decent understanding of the device from the user's perspective. This program should also include complaint handling procedures to address and collect reported issues. Whether the cause is due to human or mechanical factors, the system should ensure the reports are circulated back to both the biopharmaceutical company and device manufacturer for further review and troubleshooting.

Another criterion to consider for the commercial market when choosing a device partner is the company's actual market scope. In other words, whether they have

experience in developing a globally launched device can determine if adequate experience will be embodied in their development and manufacturing processes.

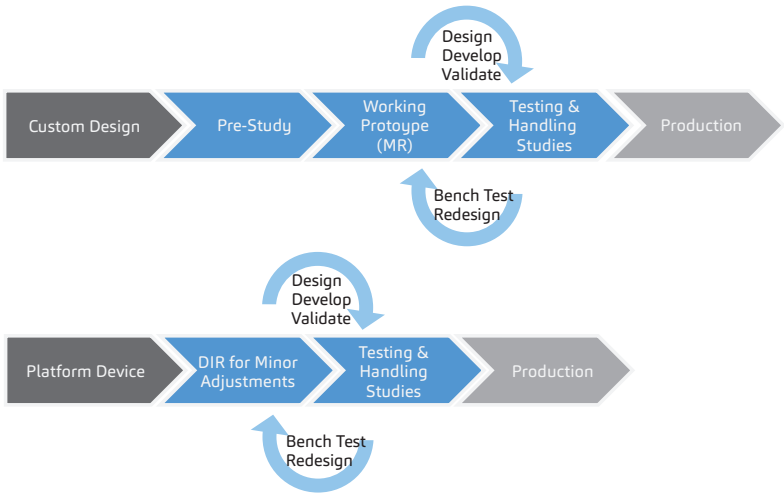
3 DEVELOPMENT

- Biopharmaceutical companies can choose to develop an auto injector based on an existing platform or develop a brand-new device.
- The decision will be mostly dependent on cost and time to market.

The administration requirements of every drug are unique depending on its therapeutic purposes. As these requirements are translated into device specifications, the decision to customize an existing platform or to develop a new device is one that the biopharmaceutical company needs to make before proceeding to development stages. With the device knowledge and experience residing mostly with the device manufacturer, an ideal partner should be capable of providing assistance in assessing which development route corresponds to the biopharmaceutical company's business model the most.

Finding the balance between cost, time and device design will be one of the major determining factors when finalizing a suitable route. Choosing an existing platform allows for further device customization, and can imply cutting additional cost and time associated with pre-study and prototype phases. A traditional development program on the other hand indicates a longer development cycle but results in a brand-new device, which may better meet market demands.

Figure 6: Development Checkpoints Part I : Custom Design vs. Platform Device



Whichever route the biopharmaceutical company decides to take to initiate the auto injector project, accurately defining a set of design input requirements (DIRs), a document that specifies the detailed requirements and purpose of the desired device, is a vital step to kick-start the development process. Such a definition should encompass key functional prerequisites that can fulfill patient needs and indicate

the range of corresponding device design required. This may include cartridge specifications, drug type, injection route, injection time, intended use, regulatory and functional requirements, risk management plan, etc. Accurately identifying these properties is only possible if the pharmaceutical company is well prepared for projects of this nature.

Finally, during the development phase, clear and constant communication is essential to a successful collaboration. In addition, a competent partner with the core capabilities to provide timely enhancements will help make the development process run more smoothly.

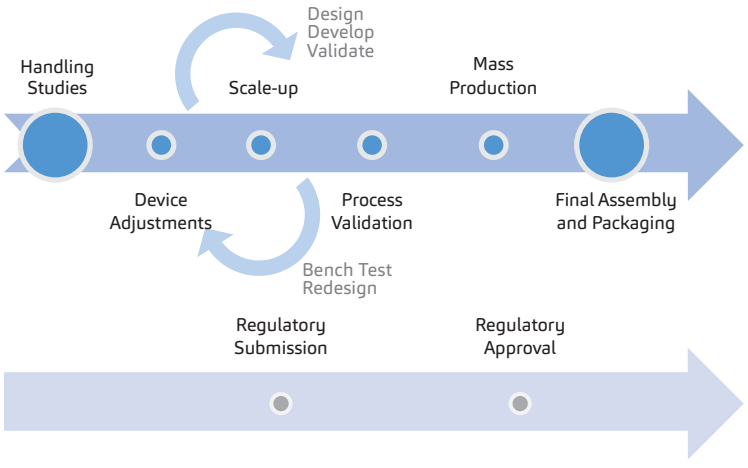
3.1 DESIGN COMMUNICATION

- A design input requirement (DIR) document specifies key functional prerequisites of the device design.
- As much as 80% of the total product life cycle cost may be determined by decisions made during early development stages (Cooper & Chew, 1996).
- The DIR will affect how critical processes and testing parameters will be set up.

The DIRs in document form will serve as a communication tool between the biophamaceutical and device companies and will be used to identify needed adjustments for the preliminary device prototype. The DIR is a living document that will also be leveraged to define critical process steps and testing parameters, ultimately affecting the setup of the subsequent manufacturing processes and related key quality attributes.

At this stage, gaps between expectations based on empirical parameters and actual mechanical executions will quickly emerge, making it imperative for the drug and device companies to hold regular meetings to discuss possible solutions. The project management teams should now act as the window of contact and coordinate this communication, holding regular sessions to ensure both parties are fully informed of any needed changes. Design control regulations will also need

Figure 7: Development Checkpoints Part II



to be applied to clearly define the design activities and changes taking place as well as when formal design reviews need to take place.

Once a preliminary device design has been agreed upon, the biopharmaceutical company can perform handling studies for the anticipated patient demographic, gathering actual user feedback for validation in a simulated environment. The collected and analyzed feedback should then be evaluated on how accurately the device executes its intended use. Sharing this data with the device partner is crucial to ensure design validation and verification are in tune and reflects the end users' needs before moving to scale-up, where more parameters will be introduced and the device enters another repeated cycle of adjustments. It is important to note here that when data from handling studies are not properly communicated back to the device company, vital user concerns may be overlooked in the design, only to be noticed in the form of user complaints after launch. Examples of shared data may range from user-preferred physical attributes, such as device color, size, label textures, to design features such as injection feedback mechanisms.

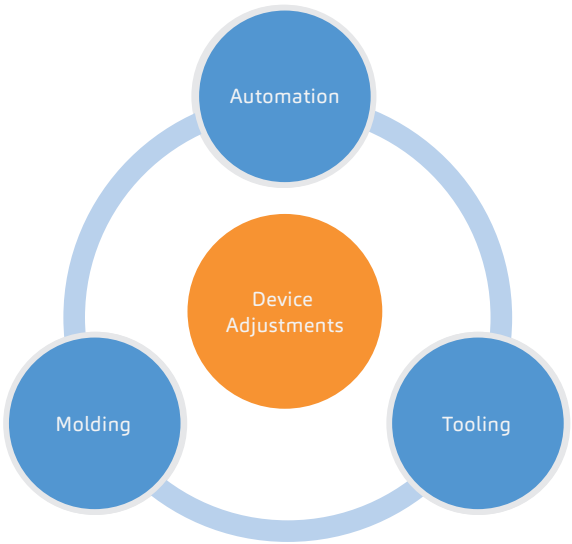
- Proper handling studies need to be performed to confirm if the device executes its intended use.
- Each device adjustment requires support from core capabilities such as metrology, CNC machining, automation, tooling and molding.
- Possessing core capabilities in-house streamlines processes, cuts costs, saves time and reduces miscommunication.

Repeated device adjustments for verification and validation during manufacturing scale-up are expected to ensure the auto injector meets specifications. With each adjustment often involving support from various capabilities such as tooling and molding, communicating new parameters accurately is vital. However, truly accomplishing efficient communication and executing changes in a timely and cost-effective manner require housing core capabilities such as metrology, CNC machining, automation, tooling and molding under one roof, as processes will be more streamlined and miscommunication minimized.

3.2 SUPPORTING ADJUSTMENTS WITH IN-HOUSE CAPABILITIES

While some suppliers already have professionals for design, testing, assembly and molding in-house, few have their own tooling and automation team to provide expert support on-site. With the crucial and frequent device adjustments required during development, owning these capabilities and expertise empower the device company to quickly address design changes while ensuring quality.

Figure 8: Supporting Device Adjustments with Key In-house Capabilities



3.3 TOOLING AND MOLDING

- Outsourcing tooling can potentially delay project timeline and lower control over quality supervision.

As it requires a significant investment to establish an in-house tooling center, some device manufacturers prefer to outsource their tooling to third-party vendors. At first glance, it may make more economical sense to do so, but this can quickly become a bottleneck during development for various reasons.

Additional time will accrue as another layer of communication is now required for every adjustment and can easily delay the project timeline. The matter of quality supervision also becomes difficult as the processes are now taking place at a different site with a different team. With the auto injector being a relatively new product, it becomes difficult to find a tooling vendor that has experience in the area of auto injector molding. Subsequently, even more time will be required to educate and oversee the processes, with the likelihood of increased error due to lack of experience.

By working with a partner with in-house tooling and molding centers and knowledgeable engineers and operators, the above issues can be significantly minimized, providing a more streamlined and time effective solution for the biopharmaceutical company. Equally important is securing the associated intellectual properties within one partner as opposed to sharing with various third-party vendors.

3.4 AUTOMATION

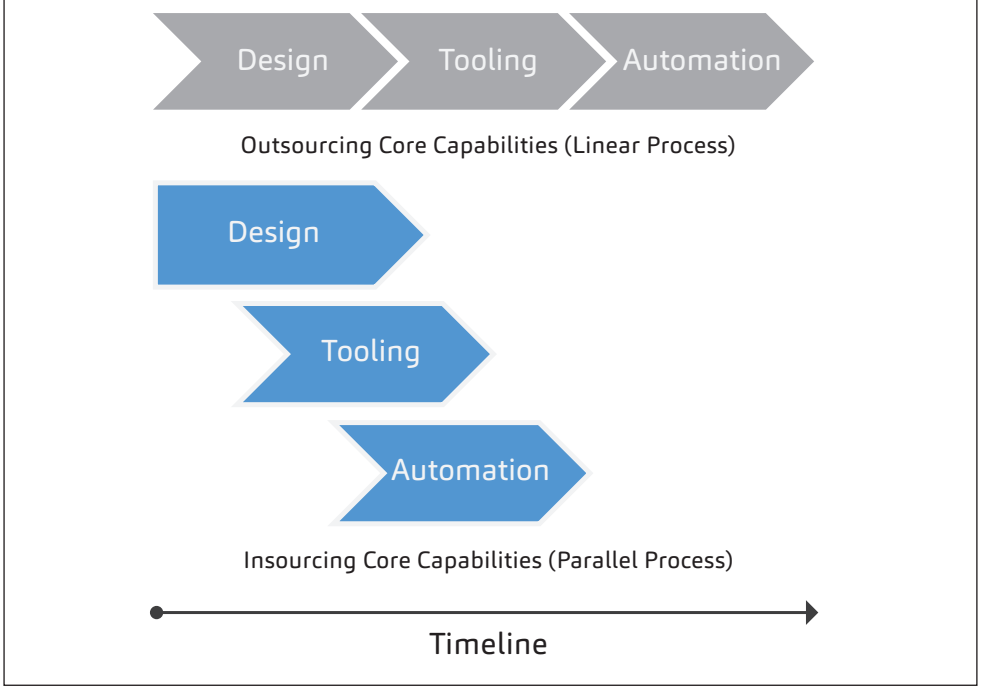
- In-house automation allows device companies to set up parallel manufacturing processes.

With the requirements of the biopharmaceutical company and the targeted user groups differing largely for every project, there are endless possibilities in the final device produced. Every product will be customized in terms of how they are tested and assembled and will be impacted by the automation capabilities available.

During the initial design phase, the device company's testing department needs to ensure the items specified in the DIR can be properly carried out and tested for verification. Unfortunately, to do so also requires a large range of custom-made fixtures, testing and assembly machines. By working with a device manufacturer that has automation in-house, drug companies can avoid the additional time needed to communicate with an external machine vendor every time a new test needs to be performed and can focus on ensuring the DIR requirements are met accordingly.

As the volumes of devices to be tested and assembled increases, how processes are set up can also quickly impact the progress of each development phase.

Figure 9: Outsourcing vs. Insourcing Core Capabilities



As seen in Figure 9, instead of executing each stage linearly, the availability of customized machines in-house allows for testing to take place once the corresponding designs and tooling are ready. Not only does this parallel process save significant time but it eliminates the additional risks and complexity associated with design and information transfers when the various capabilities are outsourced. The machinery required at each stage will vary depending on production and facility needs and will involve a team of automation experts for support on a regular basis.

3.5 FINAL ASSEMBLY

Depending on the biopharmaceutical company's business model for the auto injector project, the choice of how the final device sub-assemblies are assembled may vary ranging from assembling themselves to outsourcing it to a filling company or a packaging company.

Assembling an auto injector requires customized equipment that may have long lead times. Consequently, having a partner that has the capability to provide assembly services in-house can provide support at the right point in time. As the choice of the auto injector's shape, material and other design aspects change, so will the design of the required assembly machine. This is where having automation capabilities and expertise in-house is ideal as customized assembly machines can be made for the biopharmaceutical company to utilize.

3.6 QUALITY CONTROL

- Quality controls such as statistical process control, product release inspection and functional tests should be implemented.

Once the auto injector design has been verified, validated and adjusted to accommodate scale-up parameters, the device is ready to enter mass production where strict quality control becomes essential. At this point the biopharmaceutical company will have to depend heavily on the manufacturing partner's facilities, experience and competency as the finalized device design is transferred to and implemented in the production environment. However, the biopharmaceutical company should be aware of the established manufacturing processes and quality standards being executed. Some of the methods employed may include statistical process control, product release inspection and functional tests to prove product conformity, which are applied to finished products or purchased materials. The quality controls of the manufacturing processes and various equipment used, as well as environmental and facility factors, must also be monitored, maintained and controlled. Well-documented procedures and inspection results should be readily available and be part of the final product release.

4 LAUNCH

The biopharmaceutical company will be responsible for the details of the auto injector's commercial launch. However, the partnership with the device company does not end here.

4.1 POST-PRODUCT LAUNCH

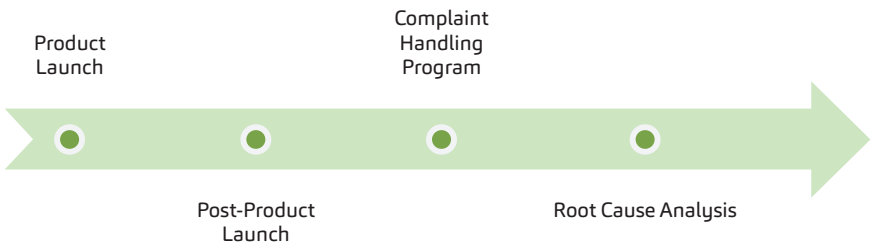
As all biopharmaceutical companies are already aware of, a project does not end at launch. It is in the nature of a commercial product that a tremendous amount of support will be required to handle post-launch issues such as the previously mentioned customer services and complaint handling programs. Ideally, the design of the auto injector at launch has already addressed the vast majority of potential issues through a carefully designed and tested DIR and various handling studies during development. Quality control measures should have also helped to assure adherence to standards.

- Biopharmaceutical team responsible for post-launch should be trained to diagnose and differentiate between issue types.
- Only potentially mechanically oriented cases should be escalated to the device company for further analysis along with variables that may have contributed to the issue.

Nonetheless, user responses are unpredictable and usage or device concerns can still surface especially with high volumes in the millions or when introducing to a brand-new market segment. To address this, the biopharmaceutical company team responsible for post-launch support should be trained to diagnose and differentiate between issue types and only escalating potentially mechanically oriented cases to the device manufacturer for further review. It is important to note that by the time the user receives the auto injector, numerous variables aside from the device's mechanical design will have been added, which could have caused usage problems. For example, the final product may have been stored or shipped in inappropriate environments, causing chemical changes in the biologics inside the auto injector. Insufficient user training or unclear instructions for use can also be a contributing factor to user complaints. Finally, a small percentage of possible mechanical related issues should be expected especially when larger volumes of devices are produced.

Properly sorting reported issues and sharing added variables can help the device manufacturer focus on replicating scenarios, addressing and justifying potential design-related device causes. The final root causes are to be well-documented in a knowledge inventory for both the device and biopharmaceutical company to refer to in the future. In addition, aside from communicating potential issues of a mechanical nature, feedback from other perspectives such as that of the biopharmaceutical's marketing team can help the device manufacturer better understand user preferences.

Figure 10: Launch and Post-Launch Checkpoints



5 CONCLUSION

When designing a combination product such as the auto injector, insufficient planning and early conceptual design vulnerabilities can easily result in quality issues, a prolonged project timeline and increased cost. It is imperative for the biopharmaceutical company to not only educate internal teams on the overall process flow of an auto injector project early on, but also to carefully choose a device manufacturing partner with an established track record, extensive regulatory experience and a wide range of in-house capabilities to support the ever-changing nature of the project.

During development, ensuring the design addresses critical quality attributes related to the device's safety and efficacy is key and can be accomplished through close communication and vigilant DIR changes, where necessary, with the device partner. Understanding all associated regulations beforehand and scheduling so that submissions deadlines do not become bottlenecks will also impact greatly on development speed and time to market. Finally, carefully analyzing and troubleshooting the device's post-launch market responses and user feedback are vital as user responses can reflect missing components not defined in the original design requirement input and be considered as an additional parameter for second-generation devices or similar projects in the future.

Mainstream use of the auto injector combination product will continue to be a growing trend in the pharmaceutical market as the demand for biologics increases and biopharmaceutical companies need to protect market share with competitive products that offer improved efficacy, convenience and safety. Understanding the associated development processes from planning to launch, required preparations and potential challenges will be the first step towards project success.

6 REFERENCES

Cooper, & Chew (1996). Control Tomorrow's Costs Through Today's Design. Harvard Business Review.

Prüss-Ustün, A., Rapiti, E., & Hutin, Y. (2005). Estimation of the global burden of disease attributable to contaminated sharps injuries among health-care workers. American Journal of Industrial Medicine.

Richter, S. (2011). Combination Products 2.0: Applying the New FDA Regulations. Agawam, Massachusetts: Microtest Laboratories.

Roots Analysis (2016). Global Autoinjectors Market 2016-2026.

US Medical Instruments, Inc. (2006). US Medical Instruments: Promoting Needlestick Prevention and Manufacturing Safety-enhanced Medical Instruments. Retrieved from US Medical Instruments, Inc.: http://www.usmedicalinstruments.com/who.html

Notes

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