



Auto-Injector Innovation

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Growing demand for self-administration devices such as auto-injectors and pen injectors is leading to ever-more innovative designs.

But in the battle to stay competitive, manufacturing partnerships that can ensure quality, compliance and patient ease-of-use are key.

Driven by the efficacy and immunogenic natures of large molecule biological medicines, the growth of biologics and biosimilars has been evident in recent years-and continues to play a major role in the pipelines of biopharma companies and their acquisition strategies.

As the need for injectable delivery solutions for use with these large molecule biologics increases, the trend for self-administration devices is showing significant growth. Indeed, the demand for devices such as auto-injectors and pen injectors has not only increased but is evolving. There is now a need for device designs to be even more innovative, while also adhering to applicable quality and compliance guidelines and, most importantly, patient needs.

As a result, it is paramount for combination product manufacturers to have a thorough understanding of established regulations-as well as to introduce technological and industrial device design innovations-to maintain market competitiveness through higher patient acceptance and compliance.

Figure 1 (page1): Innovating within the quality compliance sphere

FDA Combination Product Definitions

The US Food and Drug Administration (FDA) defines a "combination product" as a medical product that consists of two or more components with any combination of drug/device, biologics/device, drug/biologic, drug/device/biologic, and so on, that together makes a single combined medical product through design, packaging or labelling.

There are four main product categories: single entity combination; co-packaged combination; cross-labelled combination; and cross-labelled combination with an approved product.

Auto-injectors and pen injectors are considered to be single entity combination products, as they comprise two or more regulated components (for example, drug/device or biologic/device) that are physically, chemically, or otherwise combined or mixed, and produced as single entities.

Manufacturing Partnerships

Although the method of collaboration for every auto-injector or pen injector project may differ, it is common for biopharma companies to work with a primary container partner to provide the prefilled syringe or cartridge inside

the device, and with a secondary packaging partner to design and manufacture the device constituent.

Each of these constituent parts is subject to their corresponding current Good Manufacturing Practice (cGMP) regulations before and after they are combined. It is vital that the biopharma companies, which will market and distribute the final combination product, make certain that their chosen partners are also well-informed about the latest compliance guidelines and consider them at all stages of development.

However, in addition to regulatory compliance, the ultimate goal for biopharma companies is to market a product that enhances patient compliance through innovative device designs that provide dose accuracy, enhance usability and improve overall safety. This is where the right device manufacturer partner can play a critical role, by not only comprehending and integrating into the device design the injection requirements inputted by the biopharma company (taking into account possible issues the primary container may have when the constituents combine), but also innovating within the sphere of applicable quality and compliance

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Fig 2. Designing devices with human factors considerations: The cap for this device was designed with a fingerprint-like extrusion to help patients with dexterity issues to enhance their grip. The cap also offers different ways of uncapping (twisting or pulling) giving the user increased flexibility with cap removal

The Final Rule

Over the past few years, manufacturers of auto-injectors and pen injectors have had to rely on the FDA's 2009 *Draft Guidance for Industry and FDA: Current Good Manufacturing Practice for Combination Products* for regulatory insights and guidelines. Fortunately, as of 22nd January 2013, the FDA streamlined the cGMP for combination products and issued the Final Rule for 21 CFR Part 4, (*Current Good Manufacturing Practice Requirement for Combination Products*) effective as of 22nd July 2013.

While the Final Rule does not create new requirements per se, it does help clarify and solidify the FDA's position on how to appropriately apply the two regulatory system (cGMP and quality system regulation (QSR)) to combination products.

Taking single-entity combination products as an example, the FDA now clearly states that the corresponding

drug and/or device constituents retain their corresponding regulatory status both before and after they are combined. For device manufacturers that already have QSR in place, some additional supplements, such as stability testing and expiration dating, would have to be supplemented where applicable.

In-House Capabilities

For the biopharma company planning to launch a drug or biologic in a combination device like an auto-injector or pen injector, choosing a device partner that already has a proven and streamlined quality system that is continuously improved is crucial, especially if the company has limited device knowledge and related experience.

The ideal device partner would not only be able to demonstrate that its quality system complies to the latest regulations, but also that its design teams are well aware of how that system affects their designs at every point of the development stage. To

achieve this in the most effective way, the chosen device manufacturer partner should have, at the very least, an in-house team of mechanical and industrial design engineers, key manufacturing capabilities (moulding, tooling, assembly, and so on) and experienced regulatory staff.

By unifying these teams, compliance can be communicated cross-functionally and applied quickly to development phases such as device verifications and validation. When needed, the design team can update required changes as well. With key manufacturing capabilities in-house, the design team can also verify manufacturability in a timely manner before any scale-up to mass production. This helps the design team understand what compliance and manufacturing boundaries to work within.

In addition, the device partner's quality system should define every requirement where there is an intent to combine constituent parts at all

stages, from design to development and manufacturing, all the way through to the actual use of the product. Some of these items include the design input requirement (DIR), design history file (DHF) and usability engineering file (all of which will need to translate and apply to their corresponding development processes.)

For example, the DHF is a body of document that is continuously updated throughout development, whereas the DIR is a consolidated document based on the customer's user requirement specifications (such as compatibility with the pre-filled syringe, injection depth and ease of activation), which translates to the device's technical requirements and is the basis of its original innovations.

Human Factors Engineering

Another key compliance item that follows the design control processes closely is human factors engineering (HFE), which is a determining factor for patient compliance (see Figure 2). Along with design controls, both the biopharma company and device manufacturers should consider HFE factors as early as the concept development phase, since the subsequent research data will determine initial user needs design input requirements.

This data will be based on behavioural data from the biopharma company's targeted patient group and, when communicated to the device design team thoroughly, allows designers to innovate when addressing specific user profiles, usage challenges, environments and more.

Take, for example, multiple sclerosis patients that will take injections from auto-injectors. The biopharma company must conduct user research to compile how pre-existing conditions, like vision problems and muscle spasms, may affect device usage and handling, which in turn allows the designer to take this into account when customising device designs or concepts. Possible solutions to this include tactile and audible feedbacks in cases that may involve vision issues, which can be translated into a mechanical design that could feature a stronger vibration and louder click before the start and after the completion of the injection.

For rheumatoid arthritis patients, an ergonomic grip design and easy removal of the device cap is inevitable due to the joint problems caused by the disease. Features such as these can be continuously improved upon and taken into consideration to reflect findings of studies, as well as to help

minimise potential user complaints.

Supporting Tools

While integrating critical HFE factors is an integral requirement to help with patient compliance, it is also important to ensure the patient/user is properly educated and informed to feel comfortable utilising self-administered combination devices.

The use of trainer devices as an educational tool is a growing trend for biopharma companies to help with patient compliance (allowing patients to familiarise themselves with device usage before any actual injection is taken. This method can help reduce patient anxiety and prevent improper use that can lead to a fear of taking future injections.)

Other supporting tools, such as instructions for use, videos and even specialised labels, can further help with patient compliance and enhance



Fig 3. Specialised features (such as an anti-slip varnish to improve grip during injection and others improving functionality related to tracking) can be integrated into auto-injector label designs



Fig 4. Maintaining key manufacturing capabilities in-house (such as moulding) allows for the scalability of production

confidence when using these devices. For example, customised labels with special materials that offer anti-slip features may help with grip when a user exerts too much downward force during injection (see Figure 3).

Quality and Innovation

A device manufacturer that houses key manufacturing capabilities such as tooling, moulding and assembly allows the designers to more efficiently and accurately verify and translate their designs into production. Although it is safe to assume that most designers always aim for manufacturability, the results during actual development testing may differ. If the key teams are not working together for the same company, this can cause delays due to miscommunication with regards to design translations.

It is more ideal to have design teams working closely with the manufacturing

teams (such as tooling) under one roof, to ensure that functionalities specified by the DIR can be quickly verified when development testing. With all device-related manufacturing in-house, design engineers will also have the advantage of verifying and validating their novel designs with critical activities such as tolerance analysis, assembly processes, material selection, and single-cavity to multi-cavity transitions (see Figure 4).

Stimulated Market

The recent introduction of numerous biologics and biosimilars, and their corresponding advanced delivery specifications, has quickly created a new segment in the drug delivery technologies market in recent years. This sector, often recognised as the combination product device technologies market, has stimulated the need to update and combine various existing regulatory guidelines, understand new patient

usage needs and advance innovative device designs.

Furthermore, biopharma companies now have to work even closer with device manufacturing partners to ensure the final device/drug combination products are not only compliant and meet patient needs, but are also innovative enough to be competitive in the market.

The ideal device manufacturing partner should have a solid quality system implemented at all development stages, and a strong team of designers and engineers that understand and follow the associated design controls while innovating devices that address HFE and patient compliance. Even more importantly, a partner with a full suite of critical manufacturing capabilities in-house allows for the designer's innovations to be realised in a verified production form.



ABOUT THE AUTHOR

Steven Kaufman is responsible for the global marketing and public relations strategy at the SHL Group, a leading designer, developer and manufacturer of advanced drug delivery devices. Steven has extensive experience in Chinese and Western management cultures, having worked for 15 years in Taiwan and five years in North America. He has a BA from the University of Western Ontario, and completed his MBA coursework in Marketing and International Business at National Chengchi University, Taiwan.

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