



OVERCOMING THE CHALLENGES COMBINING INJECTABLE DRUG WITH SELF-INJECTION DEVICE

Continued growth in the demand for self-injection devices such as auto-injectors is putting increased pressure on biopharmaceutical companies to establish in-house device teams and external consultants with expertise in related areas. In addition, top executives are requiring their teams to be on the lookout for suitable partners in the device field and to keep abreast of trends and “what’s new”. Here, Steven Kaufman, Vice-President, Marketing, SHL Group, talks openly about a broad range of challenges that biopharmaceutical companies and their partners will likely face on the road to taking their biologics, biosimilars, generic injectables and even biobetters to market in combination products. After introducing these challenges and some potential solutions, he also touches on the importance of participating in innovation programmes with partners and related learnings.

When attending conferences such as the upcoming PDA, Pharmapack and DDP events (Figure 1), device companies such as SHL will staff their booths with experienced business development staff as well as industrial and mechanical engineers. In many

cases the topics discussed will focus on the existing pipeline of launched auto-injectors and pen injectors with one of the key questions being asked being: “What’s new?” These events are good opportunities to connect with current and potential customers,



Figure 1: SHL will be at the upcoming PDA, Pharmapack and DDP conferences.



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as well as to network with a vast array of sub-suppliers. Discussions are polite but people will often choose their words carefully and hesitate to go into detail about potential bottlenecks. Thus, as it would seem that we don't often get the chance to talk candidly about the many challenges that are faced in any typical device project, I thought it could be very useful to highlight a few challenges here, and to share some comments from others involved in supporting the industry.

PRIMARY CONTAINERS: PREFILLED SYRINGES, CARTRIDGES & STOPPERS

Before looking at establishing a device project, biopharma companies have often selected a prefilled syringe (PFS) or cartridge for their drug. In recent years, we have seen increased demand for better control of PFS and in particular making them more compatible with auto-injectors. Needle gauges such as 27G/29G thin-wall are becoming more common and it is well established that the gauge itself and the quality of the needle will impact injection time, as does the viscosity of the drug. A range of Rigid Needle Shields (RNS) are also being proposed by an increasing number of suppliers. Stoppers with coatings that improve glide force and offer other benefits are being used more frequently as well. With all of this to consider, biopharma companies must address the challenge of choice and cost. New biotech glass PFS and plastic PFS can offer increased security and would appear to be a good fit with some of the next generation devices coming to market.

Standard PFS (Figure 2) have been getting a makeover and many are now introducing biotech versions of their PFS. Manufacturers are developing products with tighter tolerances, specifically designed for auto-injector applications.

While recently visiting the production facility of OMPI in Italy, I asked Alessandro Morandotti, Front End Technical Manager, to comment on this trend and what chal-

Figure 2: Standard PFS have been getting a makeover and many manufacturers are now introducing biotech versions of their PFS.

lenges they are looking to overcome. He replied: "Containers like cartridges and syringes have become a critical part of the device optimisation for self-injection devices like auto-injectors as part of an effort to minimise assembly and functional issues. To address this, we worked closely with various biotech pharmaceutical companies and drug delivery device manufacturers to develop the Nexa PFS [EZ-fill™] platform, which tackles many of the critical issues encountered during the combination of drug primary packaging and delivery system. It minimises the potential interaction coming from contact with the glass, needle, needle glue, needle shield, plunger, and silicone oil used as lubricant inside of the syringe barrel. The flange and shoulder have a high degree of resistance and we

the primary container becomes less of a challenge as more companies look to launch their drug in a self-injection device.

TESTING, TESTING & MORE TESTING

One of the more interesting challenges related to the testing of your PFS or auto-injector is knowing what to test and how much to test. And even then, you need to have enough of the product, API in primary container and later devices, to test at the right time. Having these capabilities in-house as a device company is vital.

Before getting too far into a device project, many device companies must look at conducting primary container characterisation. Basically, they will request samples of API, several batches ideally at different timespans, from the biopharma company. The biopharma company should get the primary container and stopper from the supplier that will be working with them when they go commercial.

The filling company will use a filling line that is representative of the filling line that will be used for final production. The device company will be looking at break-loose and glide force to help establish the profile of the PFS or cartridge and to then use this

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also have tight flange dimensional control. Another vital advantage is gliding performances, since it was developed based on a specific profile where superior force performances were studied while considering the application of a polymeric-coated plunger stopper."

Other key players in the industry are offering a range of solutions to ensure that

data to optimise the powerpack or spring of the device. Most device companies utilise a broad range of equipment such as Instron and customised equipment like COIS (Completeness of Injection Stroke) that is made for SHL Medical by SHL Automation. Regardless of the equipment used, it's essential that qualified staff are available to inter-



Figure 3: Testing of auto-injectors will require the use of a standalone machine or the use of a standard Instron with customised fixtures and a vision system.

pret the results and make recommendations to the device development teams.

Testing of auto-injectors will require the use of a standalone machine or the use of a standard Instron with customised fixtures and a vision system as shown in Figure 3. Force testing equipment performs functional testing on devices such as cap removal force, injection depth, injection time and needle cover override forces.

More recently, one new test has been added to the mix. ZebraSci (Temecula, CA, US) developed a non-destructive method of evaluating the uniformity and amount of silicone oil in primary containers. This

data has been correlated to device performance and break-loose and extrusion test data. Now, primary container suppliers, fillers, device companies and biopharma companies themselves are purchasing the equipment to help mitigate a known risk of inadequately siliconised syringes.

ZebraSci has developed a lab system that can both lubricate and analyse the lubricant layer in seconds. Now customers can test a range of siliconisation amounts and distributions with their drug product and device combination (Figure 4). These tests will give the customer useful data to provide a specification to the device and syringe

supplier. Once this specification is derived, ZebraSci's high-speed analysis system (600 parts per minute) can inspect 100% of syringes produced or filled to ensure gliding force and device performance as it relates to the quality of dispersion and control of amount of lubricant.

ZebraSci President Rob Schultheis commented: "Over the years we have developed a standard which is correlated to glide force and device performance. This standard can help to resolve any glide force or device issues related to poorly lubricated syringes as it is a scalable technology from lab to production floor."

ZebraSci has been making in-roads in the market and is now found in the testing labs of CMO fillers, primary container suppliers, device manufacturers and also biopharma companies. New solutions are available for non-destructive testing of syringe siliconisation.

HUMAN FACTORS

Gone are the days of human factors (HF) testing being a "nice to have". It is now clearly a "must have". But one of the key challenges related to HF testing is identifying which organisation is qualified to conduct the HF testing. This organisation will also need to have a clear understanding of regulatory practices and the ability to write a systematic and comprehensive report. Biopharmaceutical companies and their device partners will need to balance the feedback they receive from this testing, with speed to market pressures to ensure that the device development programme stays on track. Be prepared that changes may need to be made to the device based on patient feedback. And to overcome this challenge some device companies are starting to get more involved in this field to get a better understanding of patient preferences and best practices.

With the spotlight now clearly on the importance of HF engineering, the ergonomics of device designs to enhance user experience and to ultimately improve patient compliance has become crucial. Regulatory guidelines, such as those provided from the US FDA and related authorities, state how biopharma companies need to conduct HF testing with a third party, and cannot rely on studies done by the device supplier. Testing done by device companies with regards to HF is generally just going to be used for reference only or perhaps marketing, if at all. The authorities require that the proposed device utilises the same PFS/cartridge that will be used commercially and, most impor-



Figure 4: ZebraSci has been making in-roads in the market and its equipment is now found in the testing labs of CMO fillers, primary container suppliers, device manufacturers and also biopharma companies.

tantly, with the appropriate patient group. Formative and summative studies will need to be conducted. Of course, special attention will be paid to labelling, packaging and instructions for use (IFU).

Dr Anthony Andre, Founder and President of Interface Analysis Associates (Saratoga, CA, US), an HF consulting firm specialising in validation of drug delivery devices, commented on the challenges of running a good HF programme, stating: “There are many more facets and skill sets applicable to a comprehensive human factors programme than most companies initially expect. Successful human factors programmes toward achieving validation with the FDA require design evaluation inputs, risk analysis techniques, solid formative testing, interpretation of test results into actionable design changes, labelling design and, of course, the sophisticated process of both planning, executing and reporting the all-important validation study. The best results are achieved when a human factors group can interact well with the device manufacturer so that together they achieve the objectives of the device for the intended user audiences. The challenges stem from two sources: a) biopharma companies that don’t understand the complexity of human factors activities required to successfully validate a new combination drug product or drug delivery device platform, and b) the failure of these companies to allow their human factors consultants to be involved early in the design process and to work hand-in-hand with the device developers.”

An increase emphasis on HF means that new devices are becoming more ergonomic and even easier to use. SHL recently implemented the feedback from several HF studies into the industrial design of some of their latest devices such as the Amber auto-injector, utilising ‘Pushclick’ technology with advanced labelling / packaging (Figure 5).

CONSULTANTS CAN HELP FILL SOME KEY GAPS

In recent years, the need to enlist the support of consultants has become increasingly important for some companies. Several new biopharma companies have no prior experience bringing a biologic to market and the same can be said of their experience with devices. Several players are now getting involved in generic injectables, biobetters and biosimilars. Therefore, as these companies expand their internal teams and start to get involved with pen injector and auto-injector projects, consultants with experi-



Figure 5: Amber auto-injector, utilising ‘Pushclick’ technology with advanced labelling / packaging.

ence in areas such as regulatory, HF, project management and more will be needed.

Although these consultants can help both new and more experienced biopharma companies with their efforts, it is important to keep in mind that device companies may have some issues providing full access to project details and the inner workings of their organisations. The primary reason for this is technical expertise and market intelligence. If a device company offers both industrial and mechanical design services, and the consultant offers the same, then the device company would be cautious providing a third party the same level of access to their staff, facilities and technologies as they give a customer. Regardless, balanced solutions are needed and clearly the right consultants can make significant contributions to help get combination products to market.

One of the firms actively involved with supporting companies getting into this area, Combination Product Partners (CPP), was asked to comment on the role that they see

for consultants working with biopharma and device companies. Company CEO Rosemary Gonzales explained, “The successful development and launch is not the end of the effort for an auto-injector programme. It is also critical to manage the lifecycle of the product according to the broader technology strategy, the evolving expectations from health authorities, and revisions to relevant international standards. The ability of a consulting company to provide effective support for both new development programmes and legacy products is a key differentiator in the sector.”

With more device companies now offering final assembly options, the next step naturally is to integrate labelling and packaging services too (Figure 6). In addition companies are looking to support in areas such as peripherals like injection pads.



Figure 6: Packaging, labelling and more.



Figure 7: The majority of new auto-injectors will be launched with needleless training devices.

SUPPORT SERVICES

Some biopharma companies are now looking to device companies to provide additional services to assist them in their efforts. With increasing numbers of companies getting in the biopharma space, certain companies will need to rely more heavily on suppliers such as device companies, filling CMOs and consultants. If successful, they will likely follow the model of building up a device team that is made up of cross-functional experts, but that will take time. In the near-term, more will be asked of the above groups.

For example, test equipment and final assembly equipment may be commissioned from device partners to set programmes up. This equipment can be located at the filling CMO, device company or the biopharma company itself.

In addition, companies like SHL have developed in-house capabilities in the areas of final assembly operations in the US, with labelling and packaging and of course training device development expertise. This will give biopharma companies more choice. They can handle some activities themselves, use external vendors or consultants or consider working with device companies that can handle more of the value chain operations. Regardless of who is performing which activity, cooperation and increased communication between all parties is cru-

cial. Multi-party confidential disclosure agreements (CDAs) are becoming the norm, and with increased pressure on timelines, a greater openness will be the only way to overcome challenges. Device companies will be required to expand their partnerships with primary container suppliers, develop closer relationships with consultants and third-party suppliers, and to retain staff that have an understanding of the key areas such as: drug, primary containers (standard, biotech & plastic), stopper/plungers, filling, mechanical and industrial design of devices, project management, HF, regulatory, testing and assembly equipment, final assembly, labels and packaging, trainers and more.

Training devices without needles are an essential tool for helping end-users become familiar with the correct handling-sequence of a device (Figure 7). These tools are now seen as increasingly important.

FUTURE CONSIDERATIONS & INNOVATION PROGRAMMES

Challenges will continue to be part of any programme, but one way to mitigate this will be to work with experienced partners. As a result, staff and their knowledge will become increasingly sought after. New staff should be given the opportunity to get involved with a range of programmes, attend various international and regional conferences and also receive advanced training courses. Mentor programmes that allow experienced staff to pass on knowledge will become increasingly important. In addition to some of the challenges mentioned, there will also be several technical challenges in the area of device development that will need to be addressed to support injectables that have higher viscosities, greater injection volumes and more.

Companies co-operate more in coming years to ensure that innovative electronic and communications tech such as smart phones and other devices (Figure 8) will enhance the patient experience. One example is the use of near field communication (NFC).

Innovation programmes can be set up in any organisation. SHL has established the “innovation initiative” in three locations: North America, Europe and Asia. With this structure, teams of experts will jointly and independently work on cutting-edge solutions to address current and future device needs. While many solutions will be developed in house, SHL will work with various partners to assist with better project integration and more. Of course this will involve the increased investment of resources, time



Figure 8: Communications tech such as smart phones and other devices will enhance the patient experience.

and money, but it will be well worth it. The initial feedback from biopharma companies about this initiative and similar efforts has been very positive. With numerous device launches planned for 2016-2020, these clearly are exciting times for the industry as a whole. Billions of dollars in injectables are coming to market in one form or another, and with increased co-operation between key stakeholders solutions will be developed and challenges overcome.

ABOUT SHL

SHL is the world’s largest privately-owned designer, developer and manufacturer of advanced drug delivery devices. We have more than 2,600 staff globally, with primary design centres in Sweden and the US, and manufacturing centres in Asia. Final assembly, labelling and packaging services for drug delivery devices are offered at our newest facility in the US.

SHL supplies auto-injectors, pen-injectors and inhaler systems to global biopharmaceutical companies. Significant investment in R&D has enhanced our broad pipeline of next-generation drug delivery systems. These innovative devices include a range of disposable and reusable injectors with fixed or variable dosing, enhanced precision and the ability to accommodate high viscosities.

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Ask about our SUPPORT SERVICES

Aside from designing, developing and manufacturing advanced injection devices, SHL provides robust services such as final assembly, labelling and packaging. Integrating value-added support services allows SHL to offer a one-stop-shop experience for customers and help improve speed to market.



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