



Insights Into Drug Delivery Device Manufacturing From Development Through Commercialization

SMC[®] Ltd.

Over the past decade, the pharmaceutical industry has witnessed the emergence of breakthrough biologics and target therapies. Whether the therapy is a new biologic or biosimilar, opportunities abound for pharmaceutical companies. With technology advancements and a greater understanding of effective treatment options, novel delivery methods are being introduced giving pharmaceutical companies a competitive edge and offering patients better solutions for their needs.

For drug delivery device engineers this opens up opportunities for innovative device solutions that meet the needs of the formulations as well as the specific patient group. Pre-filled syringes remain a viable option for applications administered by healthcare professionals. Patients who self-inject are faced with challenges due to the very disease they are managing, such as limited joint mobility from rheumatoid arthritis, or vision limitations from migraines, or the successes of an emergency injection when under stress. For these patients as well as others, sophisticated patient-centric devices are being introduced and embraced.

In the past, pharmaceutical companies viewed the drug delivery device as a secondary effort. It is easy to understand this since many drug delivery devices by definition are secondary packaging. This approach often left little-to-no time to develop the optimal drug

delivery solution for the patient. Device engineers were forced to use existing technologies to meet the established timelines, which in turn resulted in less than ideal device solutions. The pharmaceutical industry has recognized this as an issue and is changing to include device teams in early stages of development. This allows the team appropriate time to design and develop an optimal delivery method to meet the needs of the patient as well as the needs of the formulation.

When developing a combination product, a greater opportunity for success exists when the device technology is optimized to meet the patient and stakeholder needs. When those needs cannot be met with an existing platform, selecting a knowledgeable team with the design, development, regulatory, and manufacturing knowledge to meet the requirements results in a robust device design with greater chance of successfully launching in the market.

The capabilities needed to evolve a drug delivery device from product development through commercial manufacturing are referenced in Table 1. Whether pharmaceutical companies outsource some or all of these phases, the device team must plan accordingly for product development, clinical trial manufacturing, and commercial manufacturing. An overview of each of these phases follows.

Table 1:

Manufacturing Finished Devices From Concept To Completion

Product Development

- Design for Manufacturability (DFM)
- Risk management and FMEA
- Develop pilot manufacturing
- Product testing development
- Supplier sourcing and qualification
- Manufacture devices for:
 - Engineering testing
 - Human factors studies
 - Usability testing
 - Design verification testing

Clinical Trial Manufacturing

- Manufacture clinical trial devices
- Process validation (IQ/OQ/PQ)
- Regulatory documentation support
- Commercialization planning
- Supply chain management
- Finalize:
 - Product specifications
 - Functional testing
 - Design freeze
 - Packaging and Labeling

Commercial Manufacturing

- FDA pre-approval inspection
- Manufacture launch quantities
- Regulatory approval
- Customer product release review
- Product life cycle management
- Scalable manufacturing:
 - Launch with pilot solution
 - Increase capacity to forecast
 - Implement semi-auto solution
 - Implement fully-auto solution

Product Development

During formulation development, the pharmaceutical company will determine the best device path forward with either a new novel device technology or a modification to an existing device platform. Whether the device team is located within the pharmaceutical company or contracted to a product development consultancy, it is important to engage the device manufacturing partner at this stage. This ensures the device is optimized for manufacturability at the projected commercial product volumes within the expected device timeline, quality, and financial requirements.

The device manufacturing partner should provide significant input on the device design. Analyzing the device from the tooling, molding, assembly, automation, and testing perspectives, ensures the design and manufacturing methods are robust for long-term manufacturing. The manufacturer should also provide the pharmaceutical company with scale-up plans for the device, including the benefits and risks associated with each phase of the product lifecycle. Part of this process includes understanding the device specifications and reviewing the design failure mode effects analysis (dFMEA). Understanding what is critical from a design perspective allows the device manufacturer to create manufacturing solutions that de-risk the manufacturing process.

The device manufacturing partner should propose the best path forward from a tooling and assembly perspective. The manufacturer should initiate a process

FMEA (pFMEA) to identify and prevent as many risks as possible. The pFMEA should be reviewed between the manufacturer and the pharmaceutical company to ensure all parties understand the areas of risk. If there are areas that have too much risk, a review will determine possible solutions to reduce the risk.

Identifying risks early allows for planning of risk mitigation solutions to create balance between risk, cost, and timeline. The device manufacturing partner should utilize these analyses to fabricate pilot tooling and equipment to manufacture devices for product testing development, human factors studies, design verification testing, stability testing, and other product requirements needed during development.

Clinical Trial Manufacturing

Prior to obtaining regulatory approval for a combination product, several phases of clinical trials must be performed to collect the required safety and efficacy data. Due to the high cost of clinical trials and the length of time to complete all phases, it is critical to have high quality fully-functional devices available for the clinical trial. This can be achieved by partnering with a device manufacturer that has the necessary quality systems, including FDA 21 CFR Part 4 compliance. Being Part 4 compliant allows the device manufacturer to handle and integrate the drug product, then perform the final combination product assembly, labeling, and packaging. By utilizing a single source to manufacture the combination product, a pharmaceutical company can reduce risk and cost, and put their focus on preparing and executing the clinical trials.

Clinical trial manufacturing should be discussed during the product development phase. **The device manufacturer should provide a robust solution to develop a device that is capable of meeting clinical trial low volume, and high quality requirements.**

When reviewing the pFMEA, it must be considered that the device could be for human use at this phase. Risks must be mitigated and controls must be in place. Examples of risk mitigation controls are proper pack-out configuration of components or implementing 100% inspection of a critical specification during assembly.

Commercial Manufacturing

It is important to start planning for commercialization as the combination product advances through each clinical trial phase to ensure the device is as robust as possible, risks have been properly mitigated, and a manufacturing plan has been put in place to ensure the tools and automation can achieve the projected volumes. Depending on the commercial manufacturing solution, the timeline to develop, design, build, test, and validate new tools and automation can exceed one year. The timeline and budget must be discussed early in the program to ensure all parties agree on a commercial manufacturing path and the point in time when the plan is initiated.

A critical decision for combination products is the location for manufacturing, labeling, and packaging. If the decision is to outsource this activity to the device manufacturing partner, all preparations for the FDA pre-approval inspection must be initiated as early as possible. All quality systems must be appropriately updated, validation activities must be robust, and an internal audit must be conducted to review and address any gaps prior to the FDA audit.

Another critical component is the launch strategy.

When developing a commercial launch strategy there are multiple factors to consider including device specifications, projected annual volumes, timeline, capital budget, and target selling price.

Launching the product as soon as practical after regulatory approval gains market and financial benefits, as well as the priceless benefits by the patients. This ideal situation can be achieved by launching with the validated pilot tools, equipment and processes utilized for engineering and clinical manufacturing. A thorough pFMEA should be conducted and reviewed together with the pharmaceutical company so all parties

understand the benefits and risks associated with launching with this strategy. Although the capacity of the initial manufacturing line may not meet the needs for future product growth, the device contract manufacturer can utilize the knowledge gained during the device development and plan ahead to provide manufacturing options to meet the quality, forecasted volume, and economic targets throughout the lifecycle of the product.

Summary

Biologics and other targeted therapies are creating opportunities for innovative device solutions that meet the needs of the formulations as well as specific patient groups. These therapies often require low annual volumes and the device manufacturing strategy must fit commercial expectations even at those volumes. Optimal manufacturing solutions should be identified to meet the quality, financial, timeline, and patient needs of the product.

Including the device manufacturing partner as an early member of the device team provides important input to ensure the device is designed for long-term robust manufacturing, risks to the product and processes have been mitigated, and a phased approach manufacturing plan is used. A launch strategy that takes into account the device specifications, projected annual volumes, timeline, capital budget, and target selling price ensures the pharmaceutical company's targets are achieved and the device launches successfully. Finding the right manufacturing partner improves the likelihood of success, and provides a significant opportunity to change and improve patients' lives.



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Biographies

Sheleagh Dougan, Business Development

Manager SMC Ltd. has over 20 years of experience in the healthcare manufacturing industry. She has worked on the development and commercialization of lifesaving combination products in both program management and business development roles. Currently, Sheleagh is leading the efforts of developing new business opportunities in the drug delivery market through existing and new customer relationships.

Meredith Canty, Director of Drug Delivery Systems, SMC Ltd. has over 20 years experience in the drug delivery space from a CMO perspective. Meredith has worked with many pharmaceutical companies, design firms, and manufacturers to launch new drug delivery devices. Her experience ranges from managing the launch of new drug delivery combination products to increasing capacity on an existing product line by more than 50 million devices per year.

SMC Ltd.

SMC Ltd. provides contract manufacturing of single-use devices for the health care, pharmaceutical and diagnostics industries. Dedicated to medical manufacturing, SMC provides full product services from initial concept through final packaged device including: program management, design and development, product manufacturing, clinical manufacturing, electronics integration, and global supply chain management.

Oval Medical Technologies, an SMC Ltd. company

SMC Ltd. can provide alternate device solutions through our Oval Medical Technologies company. Oval delivers superior single-use subcutaneous and intramuscular autoinjector platforms that are patient centric with clinical advantages. Oval's device technology has the capability to deliver a wider range of formulation viscosities, both high and low volumes, and fragile molecules. Oval's approach to device development combines a deep understanding of patient need, allowing us to customize our platforms and create devices for any patient or formulation.

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