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How Pacira Pharma is working to help curb the opioid epidemic

Poorly managed postoperative pain can have a significant impact on a patient's recovery. For example, it can put them at risk for medical complications, including deep vein thrombosis, pulmonary embolus, and pneumonia.[1]

In addition, today's methods for drug delivery often introduce a drug into the body in large quantities where it must then systematically travel until it reaches the intended area. This wide-scale distribution increases the potential for harmful side effects and requires a higher cost for care due to the amount of drug needed.

Another concern about the impact of poorly managed postoperative pain is related to the use of opioids for pain relief and a rise in the misuse and abuse of these drugs by patients.

In a recent study from Stanford University, researchers found that patients undergoing 11 of the most common types of surgery were at increased risk for chronic opioid use.[2] The increased use of opioids after surgery has caused a cascade into the abuse of prescription painkillers, and opioid dependence rose more than 3,000 percent from 2007 to 2014.[3] According to AddictionCenter.com, there are an estimated 4.7 million people in the United States dependent on painkillers.[4] To address this epidemic, the FDA assembled a task force in 2013, which, among other efforts, encouraged the development of abuse-deterrent formulations of opioids. However, the most effective way to stop opioid dependence is to eliminate the use of these highly addictive drugs after surgery altogether. This was the goal of Pacira Pharmaceuticals, a specialty pharmaceutical company focused on the development of non-opioid products for postsurgical pain control, when it developed its injectable suspension, EXPAREL®.

Changing the standard of care

EXPAREL is a local analgesic utilizing bupivacaine in combination with the product delivery platform DepoFoam®. DepoFoam is made of microscopic polyhedral particles composed of numerous non-concentric internal chambers that encapsulate a drug. These discrete chambers are separated by lipid membranes and filled with an aqueous solution of a drug. Once the drug is inside the DepoFoam technology and injected into the patient, their body begins to break down the lipid membranes. This is a naturally occurring process that releases the drug without altering its molecular structure.

DepoFoam permits both systemic and local delivery, which means the platform can release drugs into the bloodstream via the interstitial space or into a body compartment, such as a joint. This targeted delivery system allows the injection of drugs into the areas of the body where pain receptors exist, focusing the administration of EXPAREL to only the areas where it is needed.

The delivery of the non-opioid drug, EXPAREL, through the DepoFoam technology provides physicians and patients with the tools necessary to overcome the challenges associated with managing postoperative pain. “EXPAREL limits the amount of drug needed after surgery, and, as a result, the potential for adverse effects is reduced dramatically,” says Ray Kaczmarek, Vice President of Commercial Manufacturing and Supply Operations at Pacira. “Most importantly, it empowers physicians to change the standard of care for postsurgical pain and ultimately gets the patient back up on their feet without the severe adverse events or the side effects of an opioid.” After it is infiltrated into the surgical wound prior to closure, EXPAREL can deliver 72 hours of postsurgical anesthesia, Kaczmarek says. This significantly reduces pain during the first 24 to 48 hours after surgery, when it is experienced the most.

Addressing the challenges of EXPAREL manufacturing

Beyond the composition of lipid components and the need for aqueous excipients, the effectiveness of DepoFoam’s delivery platform is dependent on the manufacturing process used to develop it. Kaczmarek says one challenge is the critical need to properly handle EXPAREL in its sterile state. “Once we start the process of creating the liposome, we have to maintain sterility assurance all the way through to the patient,” he explains. “That means the bulking process, the filling process, and everything done until the point where the physician begins to utilize the drug.” Other important factors for the successful manufacturing of EXPAREL include temperature, agitation, and the design of the sterility assurance package around the drug.

What also makes the manufacturing process for EXPAREL challenging is the need for a manufacturer to understand the complexity of the drug’s critical process parameters and how they interrelate to each one of its attributes. If any one of the parameters is changed, the drug product will either fall apart or will not work in an appropriate way. Additionally, the limitations of today’s downstream technologies create a manufacturing bottleneck that makes the scale up of EXPAREL difficult. “The sooner the industry starts improving downstream technologies, the sooner we will be able to maximize the technologies, such as TFF [tangential flow filtration], to improve our manufacturing scale,” explains Kaczmarek. “Until then, we’re creating newer platforms and utilizing different technologies to allow the maximization of scaling by limiting exposure in the downstream process and implementing continuous batch processing.”

It was these challenges, as well as the need for global exposure and regulatory compliance, that caused Pacira to seek a partner who could provide them with the resources and experience necessary to build upon their existing manufacturing capacity to successfully manufacture and globally commercialize EXPAREL. After vetting other prospects, Pacira decided on Patheon pharma services. Kaczmarek says what was particularly appealing about Patheon pharma services is that the relationship between the two companies is not a typical CDMO/sponsor relationship. “I’m not just handing the drug product over and then hoping they manufacture and provide the supply to me,” he explains. “We’re working together to transfer a complex manufacturing process into one of their suites, and then, within that work, expanding the process out and training their personnel on how to run it. We will monitor the process as a partner as they manufacture the drug product.” This is accomplished through the use of Patheon pharma services’ condominium manufacturing model. The “condo” model is one of six adaptable manufacturing arrangements the CDMO offers its clients. Through multiple options, Patheon pharma services provides sponsors with a variety of flexible and scalable manufacturing approaches to create the optimal solution to fit a client’s needs.

A stronger partnership through collaboration and communication

Patheon pharma services' condo model is designed for companies either expanding their current manufacturing capacity or introducing new product with unique characteristics that cannot be manufactured on a conventional manufacturing line, such as EXPAREL. In addition to providing manufacturing design services, the team works with equipment suppliers, validates the processes, builds the line, and manages operations on behalf of the client. Overhead is shared, and the line can operate as needed to meet demand.

Kaczmarek says Pacira personnel support the manufacturing and quality assurance processes in the UK facility. "This gives us the ability to utilize the facility, the staffing, and the support structure Patheon pharma services brings to the table," he says. "They also have multiple areas outside of the U.K. facility where we can continue to grow strategically." Kaczmarek adds that Pacira wanted a manufacturing agreement and strategic partner, not just a one-time partner for one product. They potentially want to utilize Patheon pharma services for their pipeline. "We want to take the new technologies we are developing and place them into their facilities, so they can be co-located with the people who are learning the processes and understanding our drug. Patheon pharma services provides the ability for us to do that through the condo model and the footprint design they have in their U.K. facility."

The condo model design coupled with the manufacturing agreement gave Pacira a high level of confidence that they not only picked the right partner, but they would also be able to control the intellectual property of their drug product design and formulation. "Other potential manufacturing groups we were looking at did not have the same type of model, nor did they have the same ability to provide that type of an operational environment where we could transfer a very complex process to them with the understanding of how they would actually be able to manufacture moving forward," says Kaczmarek. As the next step toward creating an even stronger relationship, Pacira and the pharma services team are establishing a governance relationship, where both companies speak on a regular basis about topics like how the U.K. facility is being utilized and whether the product is being fully commercialized in an appropriate way. "Their openness to the integration of these types of technologies into their network maximizes Pacira's ability to supply EXPAREL to patients, as well as our future pipeline," says Kaczmarek. "By having these strategic discussions and agreements, it minimizes the cost of manufacturing for both companies and it maximizes the ability to provide patients the quality drug products in a very timely manner. Ultimately, that's what we want to be able to do, and both companies are coming together to make that possible."

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