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**Collegium pharmaceutical’s approach to abuse deterrence breaks new ground**

Opioids have been utilized for centuries and remain the most powerful analgesics available today. Their use in the treatment of chronic pain is strongly supported by leading pain experts, the American Pain Society, the American Academy of Pain Medicine, the U.S. Federation of State Medical Boards, and the Centers for Disease Control and Prevention.<sup>1-7</sup> It is estimated that 100 million Americans currently suffer from chronic pain, and many of these patients rely on daily opioid regimens to control their pain and improve their function and quality of life.<sup>4-8</sup> However, given the intrinsic qualities of these medications, they are not without significant risks, namely those of abuse, misuse, and diversion. The abuse potential of these products is, in part, responsible for the opioid abuse epidemic, which is a serious, ongoing public health crisis.

Prescription opioid medications, particularly extended release (ER) formulations, have been criticized, due to their high drug load per tablet/capsule and for the ability of abusers to manipulate the products. Manipulation of the route of administration of these products, such as chewing, crushing, breaking, snorting, or dissolving for intravenous injection, results in a greater and faster “high” for the abuser. In the case of ER formulations, this is of even greater consequence as they contain a 12- to 24-hour dose, rather than a 4- to 6-hour dose as an immediate release (IR) formulation does.

In an attempt to balance the critical need of opioids for patients suffering from chronic pain with the opioid abuse epidemic, the United States Food and Drug Administration (FDA) called on the pharmaceutical industry to make safer opioid products, including abuse-deterrent formulations (ADFs). Abuse-deterrent products, including Xtampza® ER, have been developed to resist the ability of abusers to tamper with the product to defeat ER properties and alter the route of administration.

## How waxy microspheres make a difference in abuse deterrence

Xtampza® ER, produced by specialty pharmaceutical company Collegium Pharmaceutical, is an oral ER abuse-deterrent formulation of oxycodone. It is designed to treat pain severe enough to require “daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.”<sup>9</sup> The capsules are created using the company’s DETERx® technology platform, which produces waxy microspheres that incorporate a solid solution of the API. The small size of the microspheres and their waxy nature prevent any meaningful particle size reduction, making it difficult for abusers to effect a significant change in the drug release profile. “We have demonstrated through both in vitro and in vivo trials that Xtampza® ER is not adversely impacted by the common methods people use to abuse opioids,” says Saim Saim, Vice President of Pharmaceutical Development at Collegium Pharmaceutical. For instance, whether someone takes the capsule intact or attempts to crush the contents, the extended release characteristics of the product do not change. The formulation design also offers other benefits, such as the ability to sprinkle the microspheres from inside the capsule onto food or directly into the mouth or administer them through a feeding tube. It is particularly useful for patients who struggle with the ability to swallow.

## A willingness to embrace risk: Collegium’s search for a partner

The DETERx® technology relies on a microsphere manufacturing process that makes use of novel equipment and nontraditional waxy excipients, which include waxes and fatty acids. The microspheres are manufactured using a novel spray congealing process. While Collegium had come up with an innovative new approach to ADFs, it did not have the capacity or resources to manufacture its drug on a commercial scale. A partner was needed that not only had the space and expertise necessary to run this unique platform but was also willing to pursue the development of a product that did not fit into the traditional manufacturing mold. “The DETERx® manufacturing process is not a standard process, so we needed a company that was open to embracing new technologies,” said Saim. “Another challenge is that, because there isn’t a commercially available unit anywhere that mimics the process used for Xtampza® ER, we needed a partner that could work with us to come up with our own design to accommodate this process. Unfortunately, equipment and process design is generally not a core competency of CDMOs in the pharmaceutical industry.”

Collegium also preferred that its CDMO be in the U.S. due to Xtampza® ER being a controlled substance, and it had to meet Collegium’s requirements when it came to capacity, infrastructure,

and experience. “The process for DETERx® requires a large room with high ceilings that can accommodate our specialized equipment,” explains Saim. “We wanted a partner that had an adequate facility and manufacturing expertise, a good history with the FDA, and a strong reputation within the industry.” After noticing considerable differences between its final contenders, the team decided on Patheon, part of Thermo Fisher Scientific. “We found Patheon was not only willing to accommodate special projects, but it also had the excitement level about ours that we were looking for from a partner,” said Saim.

In addition, Saim says that, while Collegium had enough funding to take its product to the next stage, the company was not established like other larger pharmaceutical companies. With just a few employees at the time, it was especially important that Collegium’s future partner would provide a small pharma company with just as much attention as it would a large one. He found Patheon very receptive in that regard. “Frankly, it didn’t take long to make the decision because we felt that Patheon had everything we needed to initiate the project and potentially expand the resulting product line,” said Saim.

To move the project forward from laboratory to commercial scale, Patheon established a team composed of a formulation scientist, a process pharmacist, a process engineer, a quality analyst, and an analytical chemist. “We faced several unique challenges with Xtampza® ER for which specific skillsets were required,” explains Yogesh Chachare, Senior Formulation Scientist at Patheon. “These challenges included Xtampza® ER’s specific equipment requirements, the implementation of a novel microsphere manufacturing process, process optimization of the intermediate steps, and a desire to assess and reassess the development progress made at appropriate intervals. However, we were able to put together a team that could deliver on the skills, science, and technology aspects needed to make the product commercially possible and viable.”

Saim says that, as the relationship progressed, he became impressed with the Patheon team. Specifically, he describes how, based on discussions about what Collegium wanted to achieve, Patheon was able to implement the novel design and provide an opportunity to expand the manufacturing space for Xtampza® ER. “We had a good team of engineers from Patheon who were very creative and could work with us to implement a new process that could successfully manufacture Xtampza® ER,” he explains. “In the pharmaceutical industry, it is not just making the product; it’s making it in a controlled fashion. And that’s what we achieved when we integrated our specialized process into Patheon’s existing infrastructure.”

## A fight worth joining

The opioid abuse epidemic is a serious public health crisis that demands action on the part of many stakeholders. While abuse-deterrent opioids will not solve the opioid abuse epidemic alone, they play a critical role in the fight against it. Xtampza® ER was approved in April 2016 and marketed later that year in five different dosage strengths. This product represents a next-generation technology. Importantly, Collegium is now actively working to apply the DETERx® technology to other opioid molecules, including hydrocodone. The impact of Xtampza® ER, and future DETERx® formulations, on real-world abuse is currently being evaluated. It is Collegium's hope that the DETERx® platform will have a meaningful impact on opioid abuse while simultaneously allowing patients suffering from chronic pain access to therapies that offer them a chance at a normal life.

## References

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