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CASE STUDY

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Fighting the opioid epidemic: how Grünenthal's abuse-deterrent technology contributes

Prescription opioid products are an important component in the armamentarium of modern pain treatment. While the wider use of opioids has led to many benefits for patients in pain, it also has led to higher incidences of misuse, abuse, and development of opioid addiction.

Extended release formulations of opioids, in particular, have become a major factor in prescription drug overdose deaths in the United States over the last 20 years. According to the Centers for Disease Control and Prevention, more than 183,000 people died in the U.S. between 1999 and 2015 from overdoses related to prescription opioids.1 It is estimated that U.S. hospital emergency rooms see more than 1,000 people each day as a result of prescription opioid abuse, and 91 Americans die daily from an overdose related to prescription opioids and/or heroin.[2]

As part of the FDA's efforts to address this growing issue, the agency put an Opioid Action Plan into effect in 2011 to "reduce opioid abuse, dependence, and overdose in the United States."[3] Part of this plan included a call to pharmaceutical manufacturers to develop and expand access to abuse-deterrent formulations (ADFs) in order to discourage abuse among patients and promote innovation in the industry.

Among other benefits of ADFs, these formulations can create a hurdle to abuse progression for recreational abusers. This is because patients often start abusing prescription drugs orally, either by chewing or swallowing them whole, but during the course of their dependency, eventually switch to non-oral routes. This typically begins with intranasal insufflation due to the nasal cavity being a thin, well vascularized tissue, which allows faster delivery through a direct route to the bloodstream. Once a user develops a certain tolerance to the intranasal route he or she then switches to intravenous injection. This can lead to other serious implications, such as the spread of disease through the sharing of needles. ADFs have the ability to inhibit this progression, thereby preventing many users from moving to the next phase of addiction, which is commonly heroin. The issue of heroin addiction is also a growing issue, as the number of overdose deaths from this cheaper, more accessible drug has quadrupled since 2010.[4]

Finally, the growth of prescription abuse and the progression of the addiction have impacted the medical community as well, creating negative reputations for both pharmaceutical companies and the physicians prescribing opioids. This black cloud over the compound class of opioids may become so damaging that, in the future, eligible patients might not have access to this valuable treatment option for pain. In fact, issues with availability have already begun to negatively impact many patients' access to pain relief medications due to some state-level restrictions[5] and rescheduling for the hydrocodone combination products.[6]

In the 2000s, Grünenthal, an international pharma-ceutical company with a fully integrated R&D, took notice of the growing rate of opioid abuse. The issue concerned the Grünenthal team not just from a perspective of patient safety; the family-owned company, focusing on innovative approaches and technologies for treating pain and adjacent indications, did not want to see the abuse of opioids prevent legitimate patients from receiving their necessary medication. The Germany-based company set out to create an ADF with a technology that creates a physico-chemical barrier to abuse and, as a result, safeguards patients from the battle of addiction.

A formulation against manipulation

Grünenthal's abuse-deterrent formulation, INTAC®, guards against manipulation techniques often utilized by prescription abusers. These usually involve pulverization and, sometimes, subsequent dissolution, of the tablets. Grünenthal developed a proprietary process using hot melt extrusion to apply heat and pressure to create a crush-resistant matrix. The resulting extrudate has the resistance and gelling properties needed to make INTAC®'s barrier successful. The process used to create INTAC® guards against manipulation while still maintaining the clinical benefit of the standard form for the patient. The result is a formulation that deters abusers but does not require the patient to take additional ingredients that do not add to their therapy or may precipitate withdrawal.

By making the formulation resistant against crushing, Grünenthal impedes intranasal abuse, because the tablet cannot be turned into a fine powder. This also prevents intravenous abuse, as abusers usually first disintegrate the tablet and then dissolve the powder in small amounts of liquid, which they subsequently inject. With INTAC®, such attempts lead to the creation of a viscous mass that is difficult to draw into a syringe. While it is impossible to completely prevent abuse, research by the CDC indicates barriers like these can reduce the progression of abuse from oral to nonoral routes.[7]

The INTAC® platform addresses various release profiles, from extended release (ER) to immediate release (IR) and a wide variety of mixed ER/IR profile (also known as modified release, or MR). Besides the release profiles, the technology also allows formulating various substance classes. Specifically, there has been a positive experience when creating INTAC®-based formulations of prescription stimulants, which is a class of drugs being used to treat patients diagnosed with ADHD. These drugs are also being abused for recreational purposes via snorting and injection.

From extrusion to the tablet: manufacturing INTAC®

While Grünenthal's core manufacturing process for extrusion is rather straightforward, it is the combination of certain excipients like polyethylene oxide (PEO) that, under hot melt extrusion, lead to the unique properties of INTAC® formulations. The proprietary downstream process uses extrusion, cutting, and cooling for the formulation of an abuse-deterrent final dosage form that can be further processed into tablets. The gelling properties of the excipients used in the formulation are maintained, thereby sustaining the barrier to injection.

During development, the manufacturing process for INTAC® presented several challenges. First, although the extrusion technology used is well known in the industry, it requires specific expertise to utilize the process optimally. Second, specialized, dedicated equipment is required to establish a manufacturing process that can run almost continuously from extrusion to the solid dose form. Third, the nonstandard downstream operations require a well-trained and educated manufacturing staff to run the process reliably. Finally, Grünenthal's ADF customers are currently all U.S.-based companies, which called for a development and manufacturing site in the U.S., to simplify the handling of scheduled drugs. To achieve these goals, Grünenthal sought out a partner with the expertise, capacity, and location that could accommodate its needs and drive the success of INTAC® in the U.S.

Making the cut

In addition to the practical needs mentioned above, Grünenthal sought a CDMO with a solid reputation in the pharmaceutical industry for its expertise, reliability, and cost, as well as a willingness to embrace the challenge of implementing a specialized technology. Grünenthal evaluated many potential partners, but few could meet all of their needs. Grünenthal ultimately selected Patheon, which was an especially appealing option due to the company's condominium manufacturing model. The condo model is one of six adaptable manufacturing arrangements Patheon offers its clients. This highly customizable manufacturing solution provides sponsors with a variety of flexible and scalable approaches to create the optimal solution to fit their program's unique needs.

For Grünenthal, Patheon and its condo model addressed each of INTAC®'s biggest manufacturing challenges. Both companies worked together to plan a layout for the manufacturing suite dedicated to the needs of INTAC®. "Because of the flexibility offered by Patheon, we were able to optimally set up the equipment in the INTAC® suite without any restrictions," explains Siegfried Ebner, Head of the Innovation Unit Devices and Technologies at Grünenthal. "In addition, operators and engineers traveled to our Aachen headquarters for training on the INTAC® equipment long before it was installed in the Patheon suite. Patheon's Cincinnati location addressed another major need for use, as it brings the INTAC® technology infinitely closer to U.S. customers, eliminating the need for further transfers. As a result of working intensively together from the beginning, Patheon's staff was ultimately able to run our equipment and processes with complete success." While distance can be a hurdle in any global relationship, the companies were able to overcome the 6-hour time difference between Aachen and Cincinnati with regular teleconferences as well as for any issues that required special attention. Meeting face-to-face on a regular basis also proved beneficial as each team believes this strengthens the relationship of all involved.

Grünenthal further continues its development of the INTAC® technology as a way to help fight against the growth of opioid abuse and protect patients from this deadly epidemic. Looking forward, the company believes its technology is suitable to raise the hurdle to abuse of other compounds, such as prescription stimulants and certain over-the-counter medications that are prone to misuse and abuse. Projects with these compound classes are under development, and research is also being done to investigate the suitability of Grünenthal's technology to impede conversion from pseudoephedrine to crystal meth. With a strong contender for widespread abuse prevention and a trusted partner on its side, Grünenthal stands strong as an innovator in pharma as well as an advocate for the health and safety of today's patients.

References

1. Centers for Disease Control and Prevention, Prescription Opioid Overdose Data – **https://www.cdc.gov/drugoverdose/data/overdose.html**
2. Centers for Disease Control and Prevention, Understanding the Epidemic – **https://www.cdc.gov/drugoverdose/epidemic/**
3. FDA, Fact Sheet – FDA Opioids Action Plan – **https://www.fda.gov/newsevents/newsroom/factsheets/ucm484714.htm**
4. Centers for Disease Control and Prevention, Heroin Overdose Data – **https://www.cdc.gov/drugoverdose/data/heroin.html**
5. ACP Internist, States aim to limit opioid prescriptions – **https://acpinternist.org/archives/2016/10/laws.htm**
6. FDA Blog, Rescheduling prescription hydrocodone combination drug products: An important step toward controlling misuse and abuse – **https://blogs.fda.gov/fdavoice/index.php/2014/10/re-scheduling-prescriptionhydrocodone-combination-drug-products-an-important-step-toward-controlling-misuse-and-abuse/**
7. J. Ziebell, presentation at Nat Rx Abuse & Heroin Summit 2016 – **https://www.fda.gov/downloads/Drugs/NewsEvents/UCM527899.pdf**

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