

## Abuse-resistant painkillers get mixed FDA response

With painkiller addiction on the rise, drugmakers have come up with clever ways to discourage such behavior. As recently as 20 June, the US Food and Drug Administration (FDA) approved a new abuse-deterrent formulation of oxycodone called Oxecta, developed by Pfizer and Acura Pharmaceuticals of Palatine, Illinois. The new pill becomes gummy when crushed, making the oxycodone harder for addicts to extract as a powder and snort for a quick, potent high. “It lends itself less well to standard practices of laypeople trying to abuse it,” explains anesthesiologist Howard Smith of Albany Medical Center in upstate New York.

Devising a better painkiller is big business. Doctors wrote more than 200 million prescriptions for opioid medications in the US during 2009. Meanwhile, the number of people entering substance abuse programs for opioid addiction increased fivefold between 1998 and 2008, and a July 2010 report from the US Centers for Disease Control and Prevention points to painkillers as the leading cause of fatal drug overdoses.

But not every ‘abuse-deterrent’ design has received a regulatory thumbs-up. On 23 June, only a few days after the Oxecta approval, the FDA rejected Remoxy because of manufacturing problems. Remi Barbier, president and chief executive officer of Pain Therapeutics in Austin, Texas, which developed the drug with Pfizer, says the companies are now working to resolve those issues.

Remoxy combines a crush-resistant technology similar to that found in Oxecta with a time-release element, so the pill is “trying to do a lot all at once,” says Sidney Schnoll, vice president of pharmaceutical risk management services at Pinney Associates in Bethesda, Maryland. “These are difficult products to produce.”

And Remoxy isn’t the first abuse-resistant painkiller to face manufacturing setbacks. King Pharmaceuticals, a subsidiary of Pfizer based in Bristol, Tennessee, pulled its formulation of morphine—called Embeda—off the shelves in March. Each pill had a core of naltrexone, which blocks opioid receptors, thus negating the morphine if the pill is crushed, but can also be difficult to stabilize as a core component.

### Tough to swallow

Many of the new painkiller formulations target addicts who snort or inject crushed pills, a group that represents 10–20% of all opioid abusers. But simply swallowing too many pills can be just as risky. An earlier formulation of Oxecta targeted this type of oral abuse, but the FDA rejected the drug in 2009. The pill, dubbed Acurox, incorporated the cholesterol drug niacin, which causes uncomfortable skin flushing. However, the FDA “didn’t feel that the added potential side effects of niacin, though benign, were worth the potential benefit in deterrence,” says Lynn Webster, medical director and

founder of Lifetree Clinical Research in Salt Lake City, Utah.

Rather than adding a deterrent ingredient or changing a pill’s response to crushing, the Californian biotechnology company PharmacoFore is developing a biochemically complex opioid formulation. The active drug compound is attached to a polymer that prevents the drug from binding to cell receptors until it reaches the small intestine. Once there, the digestive enzyme trypsin activates the molecule, releasing the drug. Trypsin isn’t found in the bloodstream, so snorting and injecting the medicine is ineffective. As a *coup de grace* against painkiller abuse, each pill is coformulated with a trypsin inhibitor that can block overdose if too many pills are taken at once (as the intestine only has a limited amount of trypsin at any given point). The drug just completed phase 1 clinical trials and “met all the endpoints that we had set,” according to Greg Sturmer, PharmacoFore’s chief financial officer.

Ultimately, clever pill design will need to be paired with therapy and monitoring to prevent addiction, says Steven Passik, a psychiatrist and anesthesiologist at Vanderbilt University School of Medicine in Nashville, Tennessee: “At the end of the day, you can develop a drug that’s like Fort Knox, but it’s still meant to deliver [relief] to people in pain.”

Hannah Waters

## Politicians get tough in wake of fatal pharmacy thefts

The street value of oxycodone continues to skyrocket, with individual pills selling for as much as \$80, according to some law enforcers. Not surprisingly, news headlines bear out the desperate, and sometimes deadly, measures that some addicts or their drug dealers will go to for these painkillers. The pharmacy robbery in Long Island, New York on 19 June that left four people dead brought the issue to the forefront of the public’s attention.

But legislators had already noticed. In May, US Senator Charles Schumer, a Democrat representing New York, proposed toughening the penalties for individuals who steal, traffic and tamper with medical products, including pharmaceuticals. The Prescription Drug Abuse Prevention and Treatment Act of 2011, now in committee, would increase the prison sentences for medical cargo theft from 10 to 20 years and permit law enforcement to wiretap suspects to collect evidence.

Schumer, who co-sponsored the bill with fellow Democrat Jay Rockefeller, a senator from West Virginia, hopes that harsher penalties will “ensure that law enforcement can crack down on

those who would steal prescription drugs in order to sell them on the streets,” he wrote in a statement to *Nature Medicine*. “We must quickly stamp out the root causes of this epidemic by addressing all of the contributing factors.”

However, it’s unclear whether the threat of longer prison times can turn the tide of robberies. Pharmacy theft increased 81% between 2006 and 2010, according to the US Drug Enforcement Administration, with 1.3 million pills stolen last year, primarily opioid painkillers such as oxycodone and hydromorphone.

“I don’t think that the panacea is increased penalties,” says Aaron Gilson, research program manager at the University of Wisconsin–Madison’s pain and policy studies group. He sees a need for a far-reaching program with better monitoring, education and drug disposal programs. “There needs to be a comprehensive or multipronged response to prescription drug crisis that we’re currently experiencing,” he says.

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