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Extended-Release PSE Points Acura At First Tamper-Resistant Formulation NDA

By Malcolm Spicer / Email the Author
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Executive Summary

Like extended-release PSE products already available OTC, a product with tamper-resistant formulation labeling must go through the NDA process. “The novelty of this to the FDA is what testing you do to demonstrate meth resistance … what labeling do you put on a product?” says Acura CEO Bob Jones.

Acura Pharmaceuticals Inc.’s work on an extended-release version of its *Nexafed* pseudoephedrine could deliver the first new drug application FDA would consider for a tamper-resistant OTC PSE formulation.

“One of the requests from [FDA] is, what’s the chemistry to make meth? That’s something new to them, so we have to go back and put together the chemistry for them and show them exactly how one makes meth,” said Acura CEO Bob Jones following a pre-investigational new drug meeting with FDA officials in September.

Acura and **Westport Pharmaceuticals LLC** market as monograph products immediate-release, single-ingredient PSE 30mg prouct in formulations resistant to the extraction of the ingredient. The extended-release, however, indication is not included in the OTC monograph. Acura’s *Nexafed Sinus Pressure + Pain* (PSE 30mg/acetaminophen 325mg) also is a monograph OTC made with the firm’s *Impede* tamper-resistant formulation.

Like other extended-release PSE products already available nonprescription, a product with tamper-resistant formulation labeling must have pre-market approval through the NDA process.

Acura’s research and testing includes determining which combination of PSE and its Impede technology meets extended-release criteria while remaining tamper-resistant.

While regulatory action around tamper-resistant PSE products has been limited to the Drug Enforcement

Acura’s Nexafed Sinus Pressure + Pain is an OTC monograph product made with the firm’s Impede tamper-resistant formulation.

Administration advising Westport not to use an extraction-proof claim for *Zephrex-D*, FDA would enter the discussion about label claims in a review of an NDA for an extended-release formulation.

“It’s a new line of thinking for the FDA as we move into the extended-release formulations,” Jones said.

“We know how to run clinical studies. We know what the FDA will accept as clinical studies to demonstrate safety and efficacy. The newness, the novelty of this to the FDA, is what testing you do to demonstrate meth resistance, and then what labeling do you put on a product that they do deem to be meth resistant?” he added.

The Combat Methamphetamine Epidemic Act requires behind-the-counter sales of nonprescription PSE products, but allows DEA to grant OTC waivers to products determined to be extraction-proof. Westport, which uses **Highland Pharmaceuticals LLC**’s *Tarex* formulation, briefly marketed Zephrex-D with the claim until DEA told the firm that the agency’s chemists produced meth with PSE extracted from the formulation (“PSE Product Makes “Highly” Tamper-Resistant Claim With 100% Out Of Reach” — *“The Tan Sheet,”* Jun. 20, 2014).

‘A Brand New Category’

Acura executives also had a pre-IND meeting in July with FDA officials to discuss the results from the firm’s pharmacokinetic and meth-resistance testing studies to determine the development path for an extended-release product.

The Palatine, Ill., firm said it intends to submit additional “meth resistant” testing information for FDA review prior to submitting an IND, as the agency recommended.

According to the firm’s quarterly report filed Nov. 4 with the Securities and Exchange Commission, FDA “acknowledged the potential value of the development of risk-mitigating strategies for new” PSE formulations “while also recognizing an approved ‘meth-deterrent’ extended release pseudoephedrine product would be novel in” OTC.

FDA officials in the pre-IND meeting did not formally state whether meth-resistant claims would be appropriate but said the agency “is open” to considering “an appropriately worded, evidence-based claim directed to the consumer and/or retailer,” Acura said in its quarterly SEC filing.

FDA for more than a decade has encouraged the pharma industry to develop abuse-deterrent formulations for opioid drugs typically indicated as painkillers (see related story online in this issue, “*“Tan Sheet”* Participates In Capitol Hill Briefing On PSE Diversion” — *“The Tan Sheet,”* Dec. 18, 2015) .

Acura also develops abuse-deterrent formulations for opioids and is on top of FDA criteria for testing needed to submit NDAs for those ingredients. But the firm is ahead of FDA on tamper-resistant PSE formulations.

“For the FDA, a lot of the chemistry and a lot of the science around meth production is new to them,” Jones said.

“We’re walking in the door for the first time saying we want to create a brand new category. We’ve already started creating a brand new category” with tamper-resistant, immediate-release PSE. “We want to extend it now with the FDA’s participation,” he added.

Acura has not set a timetable for filing an IND and later an NDA, largely because its project is FDA’s first exposure to tamper-resistant PSE formulations.

“As with anything that’s new and leading edge, it takes long,” Jones said.

“We have to digest everything that they’ve advised us on. I think this will be an incremental approach.

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Companies
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Highland Pharmaceuticals LLC
Bayer AG
Bayer Corp.
Bayer HealthCare LLC

This won’t be so much as a typical pathway for us where you go, okay, we got it, we open an IND, we do all the research, submit an NDA and we’re good to go. I think we’re going to piecemeal this into the FDA, and have a continued dialogue with them as to how this works.”

Tamper-Resistant Delivers Results

Regardless of Acura’s progress on its pre-IND work and whether FDA eventually approves an NDA for an extended-release Nexafed with tamper-resistant labeling, immediate-release PSE products in tamper-resistant formulation already are making a difference in curbing diversion of the ingredient in West Virginia.

Nexafed and Westport’s Zephrex-D were accounting for 62% of nonprescription PSE product sales in the state through September, and about 1% of sales in other states. Some West Virginia drug store chains and independent stores sell only tamper-resistant, single-ingredient PSE products, while others offer those along with conventionally formulated brands and private label products ("To Curb PSE Diversion, Retailers Lead By Example With Emphasis On Tamper-Resistant Products" — *"The Tan Sheet,"* Sep. 19, 2014) .

“What we’ve seen between 2013 and 2014 in West Virginia is a 40% reduction in meth lab seizures. And we’re trending off another 20% this year,” Jones said.

“West Virginia is now a real-life laboratory of what you do if we move to meth-resistant products. And we’re seeing very dramatic reductions in the meth lab seizures,” he added.

“The newness, the novelty of this to the FDA, is what testing you do to demonstrate meth resistance, and then what labeling do you put on a product that they do deem to be meth resistant?” – Bob Jones, Acura CEO

Moreover, the reductions are the result of tamper-resistant, not extraction-proof formulations.

While PSE can be extracted from Nexafed and Zephrex-D, it is much less than the amounts of the ingredient that can be removed from conventionally formulated PSE products.

Meth cooks, Jones says, are buying other brands of PSE products, including extended-release products, and making meth, even with the daily and monthly limits on pseudoephedrine purchases imposed by the Combat Meth Act, or the more stringent caps some state and local governments have set.

“Get over the fact that you can still make meth with” tamper-resistant products,” he said. “We know you can make meth with these products.”

Acura scientists say they could prevent extraction of 100% of the ingredient drug by formulating it with titanium capsule. “We’ll guarantee nobody will make meth with it, but nobody’s going to get any treatment for their allergies either,” Jones said.

The firm sees making extended-release PSE OTCs available as a key step in further curbing diversion of the ingredient.

“In order to head that branch of the tree off, we’ve got to get with the FDA and start working on extended release formulations and plug more of the gaps,” Jones said.

Acura licensed its Impede technology in June to **Bayer HealthCare LLC** and will jointly develop a product for the U.S. market with the **Bayer AG** business, with an option also to negotiate for a worldwide license for additional products ("Tamper-Resistant PSE Takes Big Pharma Stage: Bayer Licenses Acura’s Formulation" — *"The Tan Sheet,"* Jun. 22, 2015).

Jones said Acura counts on its Rx formulations as primary revenue drivers but it can realize greater income in the nonprescription space by licensing Impede to a larger firm.

“We don’t have deep pockets for advertising. We don’t have market clout that somebody like Bayer has. So, we always looked at this as if someone steps up who’s willing to bring technical capabilities to the mix to help us out with some of the more technically challenging products, and they shared kind of our vision in terms of revolutionizing the pseudoephedrine market to get it to be a meth-resistant marketplace, we would always consider a partnership,” he said.

The promotion of tamper-resistant formulations to impede PSE diversion is not without detractors, though. The Consumer Healthcare Products Association maintains consumers should have a choice of OTC brands to buy, and the Asthma and Allergy Foundation of America in July published results of a survey it commissioned showing that most consumers in Illinois, Indiana, Oklahoma, Tennessee and Missouri would oppose not having a choice of single-ingredient OTC PSE products at their local

grocery or drug stores ("Allergy Group Advocates To Maintain Pseudoephedrine Product Choices" — *"The Tan Sheet,"* Jul. 20, 2015).