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US FDA's ACNU Proposed Rule Played Petros Pharma's Tune To Attempt OTC Switch Of ED Drug

by Malcolm Spicer

> For ED products, "where you have a contraindication for current use of nitrates, this enables you now to leverage technology to help assist the consumer without a physician intermediary to appropriately self-select. Yes, music to our ears, we loved it," says president Fady Boctor.

Erectile dysfunction drugs haven't generated the most noise as likely OTC switch candidates with the US Food and Drug Administration moving toward making digital labeling part of its regulatory framework to make more ingredients available nonprescription.

For *Petros Pharmaceuticals, Inc.*, however, the FDA's "additional conditions of nonprescription use" proposed rule is a symphony of encouragement to develop an OTC switch application for its ED drug Stendra (avanafil).

"That was music to our ears," says president and chief commercial officer Fady Boctor.

"What it basically says is for products like this class of medication, where you have a contraindication for current use of nitrates, this enables you now to leverage technology to help assist the consumer without a physician intermediary to appropriately self-select. Yes, music to our ears, we loved it," Boctor told HBW Insight.

The FDA's June 2022 ACNU proposed rule could help ED drug firms reach the OTC market by adding information accessed digitally to labeling consumers use to determine if they should use a drug. The information would include questions on whether a consumer uses Rx drugs or has diseases or health conditions contraindicated for certain OTC drugs.

For Petros and other ED drug firms, the contraindication question would be about men using

nitrate drugs for heart conditions.

Petros looked into labeling for a nitrate contraindication with two self-selection studies it started in late 2021, one with men from the general population and the second with nitrate medicine users. (Also see "*Petros Includes Nitrate Patients In OTC ED Drug Self-Selection Studies*" - HBW Insight, 20 Jan, 2022.)

"It's the reason why this class has not seen the daylight of OTC along with potentially cardiovascular comorbidities. Those will continue to be the things that we'll confront. Nobody's overcome them," Boctor said.

FADY BOCTOR: "MANY MEN MIGHT HAVE A PRECURSOR CONDITION SUCH AS ED, AND THEY'RE NOT ENGAGING WITH THEIR HEALTH CARE PROVIDER MOST LIKELY." *Source: Source: Petros Pharmaceuticals*

"Nevertheless, with the technology inclusion, we have a fighting chance. We believe that some of the advancements in our technology that we're undergoing today, in collaboration with the FDA, that we're going to be able to resolve those issues in the coming months, and hopefully no longer than is necessary, but in the coming months. ... The problem hasn't been resolved organically. The problem may be resolved by the utilization of technology, which we've been hard at work out for now at least a solid year."

Actual Use Trial A Year Away

In that time the New York firm has completed a second pivotal label comprehension study, leading to preparing to launch before the end of 2023 its first pivotal self-selection study with digital labeling. It expects to meet again with the FDA about its switch project in early 2024. (Also see "*Petros Plots Next Point On OTC ED Switch Path: Stendra Self-Selection Study*" - HBW Insight, 20 Oct, 2023.)

"We fully anticipate we'll have to do a second pivotal selection study. We hope and are targeting to the best of our ability that we get to the end of next year and are in a position to submit our [proposal to FDA] for an actual use trial that could come by the end of '24, or very early '25," Boctor said.

He noted that proceeding further switch studies for Stendra, available Rx in 50-, 100- and 200-mg doses, depends on FDA approval. The agency has been supportive so far about Petros's initiative while keeping potential risks in view.

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“I think that they are absolutely committed to a concern around cardiovascular comorbidities. And within that umbrella, they're especially concerned with nitrate concomitant use. But also, recently, they've indicated what about patients that also have risk of stroke or heart or heart failure?” Boctor said.

“We understand, we get what they're saying. They said it loud and clear. Those are probably the most critical,” he added.

The agency also has other risk questions, “secondary items on their list,” he said. “How do you prevent abuse? How do you prevent the 16-year-olds and the 17-year-olds from walking into a CVS or Walgreens, gaming the system as bad actors gaming the system and getting product from the retail shelf without a physician intermediary.”

The digital self-selection process also would produce a digital code indicating that a consumer is cleared to buy an ACNU-approved drug. The process should prevent customers under 18 from obtaining clearance to buy nonprescription EDs by including a proof of age requirement.

Customers with cardiovascular and metabolic comorbidities signaling risks for using EDs should be denied nonprescription sales through the digital self-selection process. Those consumers, though, still can ask their physicians for prescriptions to the OTC product as the FDA’s proposed rule would allow ACNU-approved switches to also remain available Rx for patients who can’t or won’t use digital labeling or otherwise would ask health care providers about using a drug ingredient. (Also see "*House Health Subcommittee Members Question Dual Rx/OTC Status In FDA’s ACNU Proposal*" - HBW Insight, 6 Sep, 2023.)

Digital Label, Patient Engagement

Boctor described the ACNU label platform Petros is using in its studies this way: “Imagine a patient engaging with an app or a QR code. And in that engagement, the patient's asked for their medical history, patients responding as honestly as they possibly can."

"We're going to make it so for every other company in this space it works to make that technology as insightful as possible to determine for the patient you are in fact appropriate, or we think you should probably see a physician because there are some indications that there are risks associated with divergence. And then the patient can then transmit."

"The technology will be customer- or consumer-directly facing, they will have a preset series of algorithms behind the questions asked. It will serve as a smart utility that helps the patient navigate whether or not they're appropriate for them.”

“That’s more important to the patient's health because [FDA officials] believe that when a

patient engages with a physician, they engage in a longer conversation about their overall cardiovascular metabolic health," Boctor said.

Licensing Label Platform Technology Considered

Petros's OTC switch work is focused entirely on Stendra, though it will later consider other currently Rx-only ingredients. Extending the use of the digital label platform it's developing in its switch initiative already is something it's considering.

"At this time, we are hyper-focused on Stendra and solely focused on Stendra. Nevertheless, in our quiet moments where we get to imagine a dream, it's not out of scope to imagine other reasons for common visits to primary care physicians," Boctor said.

"We would love to be able to search for in the future, if this platform continues to show promise, things such as migraine, urinary tract infections, potentially depression, anxiety, and the list goes on. There is a significant pool of options."

Petros's platform for ACNU labeling so far has shown it will deliver on the demands FDA has identified, and likely would work in digitally enhanced labeling for other indications, Boctor added.

"Our ability to educate the patient, our ability to initiate a conversation around a broader health story, our ability to mitigate for concomitant nitrates and our ability to advise and guide against comorbid conditions outside of a physician in utilizing this drug, I think will help us answer their calls and I think will make the difference."

Expanding ED Drug Access A Public Health Need

Although Petros and other drug firms see ED drugs as promising switch candidates, drugs for treating other chronic conditions such as high cholesterol and diabetes could be considered by the FDA as more important for being available nonprescription.

> ***The FDA, according to its latest semi-annual regulatory update, expects to post an ACNU final rule in April 2024 – docket FDA-2021-N-0862.***

Petros has been impressed in its discussions with the FDA, though, that the agency sees expanding access to ED drugs as a public health need.

“We're grateful that the FDA had indicated that among their goals is to address sexual dysfunction across the country. They believe that's an important frontier to be involved in,” Boctor said.

That’s largely due to ED being a precursor of serious cardiovascular conditions such as coronary artery disease or cardiovascular condition and comorbidities.

“If you look at the ED space of 30 million men suffering from erectile dysfunction in this country, even with hundreds of millions of dollars [in sales] and over two decades of Viagra and Cialis being available, it's been estimated that only 25% of men have actually sought prescription therapy,” Boctor said.

“This means that many of these men might have a precursor condition such as ED, and they're not engaging with their health care provider most likely. So, they're walking around with silent coronary artery disease, which in a few years could result in a heart attack and a first cardiovascular event.”

Even though avanafil and other ED drugs have been available in the US with strong safety records, the FDA, as Boctor noted, isn’t likely to pass on requiring an actual use study with a switch NDA. However, a requirement for an actual use study for a switch NDA makes the sponsor eligible for three-year market exclusivity if a drug is approved for nonprescription sales.

“That is three years with no generic competition,” Boctor said.

And approval for generic equivalents would be a process more complicated than drug firms currently must fulfill.

Generic equivalents of switches and other brand name drugs approved through applications must use the same Drug Facts label as the original as well as match the formulation for approval. The FDA explained in the ACNU proposed rule that generic copies of ACNU switches must have a digital label platform as effective as the original’s, a bar likely higher than copying the DFL. (Also see "*Proposed Rule Making More OTC Switches Likely In US Makes More Tools Necessary For Sponsors*" - HBW Insight, 28 Jun, 2022.)

“We think that technology may be another barrier to entry, because we do believe that the generic entrant could leverage the molecule and the data behind the molecule, but they'll have to establish their own technology utility as well. And that might be an additional barrier to entry, in addition to the three-year market exclusivity,” Boctor said.

While all ED ingredients remain Rx-only in the US, an FDA-regulated product indicated for the indication is available OTC. The agency earlier in 2023 approved the first OTC ED therapeutic

product, UK firm Futura Medical plc's Eroxon gel containing water, ethanol, propylene glycol, glycerin and carbomer potassium hydroxide. (Also see "*ED Indication Reaches US OTC Market With FDA Approval Of UK Firm Futura's Eroxon Gel*" - HBW Insight, 20 Jun, 2023.)

Germany's drugs regulator earlier in 2023 remained unconvinced about OTC sales of ED ingredients sildenafil and tadalafil due to concerns about consumers buying the products despite not needing them and about misuse of the products. (Also see "*Why Did Germany's Switch Experts Reject OTC Tadalafil And Sildenafil (Again)?*" - HBW Insight, 30 Aug, 2023.)

Sanofi, on license from innovator *Eli Lilly and Company*, long has touted Cialis (tadalafil) as a switch candidate. But a planned actual use trial to support OTC use was placed on clinical hold by the FDA in May 2022 "due to matters surrounding the protocol design"; the firm is working to satisfy the agency's concerns and start the trial. (Also see "*Sanofi Hopes UK Cialis Launch Will Illustrate US Switch Potential*" - HBW Insight, 3 May, 2023.)

UK firm *Viatris Inc.*, launched in 2020 with the merger of *Mylan Pharmaceuticals Inc.* and *Pfizer Inc.*'s Upjohn unit as a generics and brand drug firm, markets Viagra (sildenafil) nonprescription in several countries including the UK and Ireland under the brand Viagra Connect and in Norway as Viagra Reseptfri. The brand which pioneered the US ED market remains Rx-only in the US. (Also see "*Viatris Retains Interest In OTC As It Spies Switch Opportunities*" - HBW Insight, 4 Oct, 2023.)

Sanofi and the former owner of the Viagra brand, Pfizer, in 2014 showed in interest in OTC switches for the drugs. Paris-based Sanofi published US survey results showing nearly 75% of men say sexual health is "critical" to their happiness; Pfizer was recruiting a "global health" brand manager with responsibilities including shepherding market expansion through an Rx-to-OTC switch. (Also see "*Cialis Or Viagra Switch? Sanofi Survey, Pfizer Help Wanted Ad Could Be Signs*" - HBW Insight, 18 Nov, 2016.)