

CRADLE OF A CRISIS

Makena, KV Pharma's drug for preventing preterm birth, has been no bundle of joy. The drug's list price triggered a hailstorm of criticism from politicians, physicians and patients. In an exclusive interview, **Noah Pines** finds how the firm has navigated the tempest and started to rebuild trust

KV Pharmaceutical president and CEO Greg Divis is drawing on his 22-year legacy in the pharmaceutical industry now as he maneuvers through the PR minefield that is Makena. The drug was approved for preventing preterm birth in early 2011, and arguably no other pharmaceutical company has faced a more intense trial since then. According to Divis, this small firm, which has been dedicated to women's healthcare for over a decade, is working through the challenges of a launch that has had lots of controversy.

Says the CEO of his beleaguered company: "What distinguishes KV is our passion about moms and babies, and our belief in Makena, the first and only medicine approved for preterm birth in this vulnerable sub-set of high-risk moms."

Divis is now applying that passion to repairing the damage done to the brand and to the company. To hear him tell it, KV faced an

unprecedented situation. Divis rattles off a stat: "Preterm birth is associated with \$26 billion in annual cost, not to mention the extraordinary emotional cost placed on the mom and the families."

Divis strongly maintains that in launching Makena, the company was responding to what was clearly an unmet need in the market. At launch, his team's focus was on educating providers on patient identification and the FDA-approved protocol for Makena, as well as increasing awareness of company resources to support access.

Published literature and his company's own market research demonstrated that there were significant barriers to access in the absence of an FDA-approved product for this patient segment, and the focus pre-approval was on how KV could address those unmet needs and help provide Makena to all clinically-eligible patients.

There had been a great deal of anticipation in the medical community for an FDA-approved version of 17-hydroxyprogesterone

The rise and fall of Makena

A timeline of major events in the ongoing Makena saga

FEBRUARY 2011

Makena approved under Orphan Drug Act, debuting at \$1,500 per treatment. A compounded version, priced at \$10-\$20, had been available for decades



FEBRUARY 2011

KV Pharma sends sent cease-and-desist letters to compounders, warning that FDA will no longer exercise enforcement discretion with regard to compounded versions



MARCH 2011

The FDA says it will not prevent compounding pharmacies from continuing to produce valid prescriptions for 17P. CMS indicates it will continue to pay for compounded versions



caproate (17P) produced in accordance with good manufacturing practices (GMP), as well as the idea that a company would be working to ensure public education and access. Indeed, before Makena was approved, there were major access barriers associated with compounded 17P, lack of a strong distribution network to get the drug to patients, and little provider and patient education.

Upon Makena's FDA approval under the Orphan Drug Act, the medical director for the March of Dimes stated, "Preterm birth is a national healthcare crisis. The approval of this new treatment is a breakthrough." But all of that goodwill seemed to go up in smoke once criticism flared over Makena's price.

Pricing backlash

Last February, KV introduced the FDA-approved, rigorously studied formulation of 17P injection at a price of \$1,500 per dose. Prior to Makena's approval, 17P was only available through compounding pharmacies for \$10-\$20 a dose.

As a result, the March of Dimes, along with doctor groups and two senators, called on KV to lower the price of Makena. Then, in an unusual move, the FDA said it would not prevent compounders from compounding 17P, rendering KV's cease-and-desist letters to these pharmacies toothless.

The FDA's position essentially gave compounders the green light to continue doing so, despite the seven years of protection from competitors normally granted to orphan drugs, and the Centers for Medicare & Medicaid Services told states that they "can choose to pay for the extemporaneously compounded [17P] as an active pharmaceutical ingredient."

Bowing to intense pressure, KV reduced the Makena price by 55% to \$690 per injection, introduced rebates and removed income caps to qualify for financial assistance. Medical societies seemed unconvinced. That month, the March of Dimes terminated its corporate relationship with KV (see major milestones in the timeline, below).

A key first step in reviving the company's reputation has been to own up to its pricing error, and to convince core audiences that efforts are under way to address concerns. "We are working diligently to demonstrate that we are on the same side of the table as these stakeholders," says Divis. "We have a common commitment to these patients. We acknowledge the missteps that the company has made and reiterated our intent to do the right thing."

Thanks in part to its efforts, KV is coming out of the cauldron. But how do you restore trust when your core audiences—physicians, medical societies, patients, the media and even elected officials—see you as inappropriately profiting from needy patients? What are the ingredients of a successful turnaround under these conditions?



KV Pharmaceutical president and CEO Greg Divis: "This situation needs to be addressed through one-on-one discussions."

A key component of its comeback has been to reestablish standing with medical societies. This has been challenging, especially in light of the accusations of profiteering levied by both the American College of Obstetricians and Gynecologists (ACOG) and the Society for Maternal Fetal Medicine (SMFM). Reinstating these third-party relationships remains essential to re-opening the door to individual MFM and OB/GYN offices that were previously shunning KV reps.

Turning point

Fall 2011 saw the beginning of a turnaround for Makena. First ACOG/SMFM issued a statement clarifying its previous statement and urging that public and private payers not limit coverage of Makena. Importantly, payer coverage had been a challenge in part due to reliance by some payers on ACOG/SMFM's earlier statement that the evidence used to obtain FDA approval for Makena was based on a study involving compounded product.

ACOG/SMFM corrected this position, attesting that the study drug used in a large 2003 NIH trial was manufactured in compliance with FDA rules for GMP (i.e., that compounded 17P was NOT used in the study). This latter point also was critical, since some of the invective hurled at KV stemmed from a perception among providers that the compounded version and not Makena was utilized in that study.

The FDA, as well, is now heading back in the other direction and may well find reason to take action against some compounders. In November the agency indicated that it would commence its own independent analysis of the bulk active pharmaceutical ingredients (API) used in the compounding of 17P.

<p>MARCH 2011 The March of Dimes, along with ACOG, AAP and SMFM, call on KV to lower the price of Makena. Senators from Minn. and Ohio ask the FTC to investigate Makena pricing</p> 	<p>APRIL 2011 KV lowers price of drug 55%, to \$690 per treatment. March of Dimes ends its relationship with KV. ACOG/SMFM issues statement, calling KV's price reduction "inadequate"</p> 	<p>OCTOBER 2011 ACOG/SMFM says its April statement was not meant to "be used by private or public payers as a basis for interfering with a treating physician's medical judgment"</p> 	<p>NOVEMBER 2011 FDA announces a review of various samples of compounded 17P, noting "variability in purity and potency." KV research demonstrates that ingredient used in compounded 17P originates primarily from non-FDA-regulated facilities in China</p>
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This action was prompted as a result of having received the results of independent laboratory testing commissioned by KV that demonstrated variability in the purity and potency of made-to-order 17P. In the notice, FDA concluded that "...as with other approved drugs, greater assurance of safety and effectiveness is generally provided by the approved product than by the compounded product."

While the pricing backlash largely drowned out KV's efforts to underscore the Makena value proposition at launch, Divis isn't taking chances with his next communication steps. Given the complexity, messages are being delivered in person, and the company is also using non-personal promotion (i.e., journal advertising, direct mail, fax, email and conferences).

"We recognize that there is a public health crisis here," Divis continues. "This is a situation that needs to be addressed through

"Today it's Avastin and Makena—which medicines will the compounders focus on next? That is unpredictable risk."

— Greg Divis, KV Pharmaceutical

one-on-one discussions, discussions that we have to evolve from one of emotion to one of facts and evidence. That is when our sincerity can come through. It's not just a press release, but it's the actions that we take as a company day-by-day."

The company has sought to place a greater focus on efforts to ensure patient access to Makena through the patient assistance and distribution program. While the assistance program had been available at launch, most providers did not have the opportunity to learn about it amidst the hailstorm of criticism from societies and the media. The company subsequently made sure that the program is available for all clinically eligible insured and uninsured patients without any income level restrictions.

Talking points

Divis' strategy also involves clarifying the value of FDA approval, which is somewhat ironic considering that FDA granted market exclusivity and then did not enforce it. KV is providing education to providers and the public about the disparities between FDA-sanctioned and compounded medications, instituting a vigorous educational effort to disseminate the following advantages:

- Approved drugs have high standards for ingredients, manufactured as a sterile injectable in a facility compliant with current GMP.
- Makena was studied in a rigorous manner to ensure both efficacy and safety.
- There is rigorous surveillance and reporting of adverse events.
- The company is permitted to produce patient- and provider-focused educational materials to ensure access and appropriate utilization.

Further, as part of the physician-focused effort, the company has underscored its commitment to HCPs by highlighting Makena Care Connection, a program aimed at reliable distribution of Makena to the orphan drug patient population; support for ongoing research on Makena; and standardized distribution of Makena through specialty pharmacies.

Other aspects of the initiative have involved education around the potential misunderstandings about compounding. KV talking

points seek to clarify that compounded medications:

- Are not generics—a common misconception among HCPs;
- Are not FDA-approved, are not regulated by FDA, and are not produced under current GMPs in FDA-regulated facilities, which can translate into dose-to-dose variability (as a result, there can be potency and sterility variation in compounded medicines, a fact that has been validated through FDA investigation);
- Are not distributed with an indication/information label, since they have not been studied rigorously; and
- Are not accompanied by surveillance or reporting requirements in the case of adverse events.

"Traditional compounding is and will be an important part of healthcare," acknowledges Divis. "There are, however, significant risks associated with compounded drugs, particularly when compounding is conducted on a large scale because more patients can be exposed to quality deficiencies. These can impact the potency of the medication, and thus the health of the patient—especially if there is little protection in place. Today it is [Genentech's] Avastin and Makena—which medicines will the compounders focus on next? That is unpredictable risk for patients, for physicians and for industry."

Finding common ground

The Makena story is still unfolding. The company faces the challenges of working to get back into the good graces of key medical societies, and thus ensuring that it can return to physicians' offices. "All great relationships are based on trust: demonstrating and delivering on your commitment," says Divis. "We have to work hard. At this stage, no one is going to grant us trust and respect and credibility—we need to go beyond. And the challenges we have faced have made that more difficult. We have to go way above."

Indeed, when Divis is asked how he would like his key customers—MFMs, OB-GYNs, medical societies and patients—to think about Makena a year from now, the CEO replies, "Whether physician or medical society, I want them to know that we are a company that is patient-committed. We listen to our customers...and we have found a common ground with all of these stakeholders, to work together, and ensure that every eligible mom can get access to Makena. We have to earn that with every single customer."

While the Makena story is not over, it is an important example of the challenges of obtaining FDA approval for existing medications that have not been previously studied systematically and/or prepared only by compounding pharmacies.

The most crucial lesson learned from this evolving case study, according to Divis, "is that when you have a talented group of people, aligned in cause, clear in objectives, you can get through any barrier, especially if you don't lose sight of what's important. What is important is our patients. They are being denied access. They are being forced to use an unregulated, untested, product that is not made under GMP conditions. We have worked tirelessly to ensure that access is there—there are now over 200 payers that have covered the product. There is nothing more powerful than a group of people who believe in what they are doing."

He primarily credits the passion of his team, a fervor which he says is infused in the company's dedication to women's health and to this group of vulnerable patients in particular. "Our belief is vital in this fight," he concludes. "These are the things that motivate us. I am very proud of our employees in terms of how they have moved and made progress on that front." ■