

## ***New, Existing Players See Opportunity In Crowded Contraceptive Space***

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By Joseph Haas

With the notable exceptions of Bayer and Johnson & Johnson, big pharma generally does not participate in the contraceptive market. (Merck and Pfizer also are in the market, although their participation occurs on a smaller scale and largely outside the U.S.)

This seems logical on its face, since the contraceptive space is mature – the first oral contraceptives were introduced 50 years ago – and diffuse – split into oral and non-oral products, with oral contraceptives divided further into combination pills that contain both an estrogen and a progestin and others that are progestin-only. As their brands came up against generic competition, big pharma largely has ceded the field to top generics and specialty pharma companies.

As a result, it has seen little incentive to innovate, finance or commit resources to the space. On the other hand, the generics companies Watson Pharmaceuticals and Teva Women's Health are aggressively expanding in the contraceptives market.

Teva and Watson are vying for the top two spots, with Teva upping the ante in late October with the €265 million purchase of Merck Serono's women's health unit, Theramex. In partnership with Merck & Co., Theramex is developing an oral contraceptive that combines natural estrogen, identical to that produced by a woman's body, with a selective progestin.

Generics companies see a good fit with this space because it is still heavily branded and is dominated by combination products, which are difficult to promote on a price-only basis. The brands enable generics companies to extract themselves from the cutthroat competition of commodity generics, and, importantly, get their names before consumers and doctors. The branding is important, moreover, because, due to short-term side effects that fade away, switching rarely occurs once patients get started on an oral contraceptive, says John Ansell, a U.K.-based consultant and former executive at Organon and Schering AG.

But innovator companies are not totally out of the running. In an era when big pharmas are looking to eke every penny out of their ongoing franchises, and small companies are struggling to find money or partners to support complex, lengthy research and development, some see signs of life. They are attracted by opportunities for new products based on incremental improvement, less intensive R&D investment and a shorter time to market.

At least three companies are taking this approach, with Bayer looking to add to its Yaz franchise (the top-selling oral contraceptive in the U.S.) with a follow-on product that includes a folate; Agile Therapeutics developing a contraceptive patch that would be applied once a week; and BioSante Pharmaceuticals, which is primarily focused on women's sexual dysfunction, working on a pill that also would address the loss of sexual desire experienced by some women on contraception.

### **Still An Attractive Market**

Contraception is still a blockbuster market opportunity in the U.S., with oral combination products holding the largest market share. Such products tallied aggregate sales of \$3.46 billion in 2009, according to data provided by IMS Health, a health care information and consulting company. By contrast, sales of oral contraceptives without estrogen totaled just \$232 million in 2009. In addition, for larger pharma companies interested in the space, emerging markets could prove to be a valuable source of revenues.

According to Al Altomari, Agile's CEO, because most contraceptive development is in the form of incremental advances with well-known compounds, a company can go into development fairly certain of what parameters FDA will want for clinical trials.

"The agency actually tells you how many cycles a woman has to be on [your drug], how much data they want," he explained. "Because we were using known ingredients, I think what FDA asked us to

do was pretty reasonable in terms of the large size of the trial. It's generally in line with other contraceptive trials that have used known ingredients."

Agile is backed by what Altomari likes to call a "gold-plated investor syndicate," which includes venture capital firms Care Capital and ProQuest Investments, as well as Kaiser Permanente Ventures. One of the factors that draws investors to contraception, he said, is the near certainty of getting reimbursement approval in the U.S.

"The market size is certainly attractive, there's nothing we see that's going to change that," Altomari said. "Managed care tends to let women have access to branded birth control – they adjust the copays. Right now, a birth control pill goes out the back door at a pharma company at about \$65 [a month], before any discounts. Well, if the woman is picking up \$35 or \$40 of that on her copay, that's not a terrible burden on the system from a cost perspective. So, brands still get on formulary, women can get access to them and I think that is certainly comforting to the investors. There's not a managed-care risk to this story."

For Bayer, the company has stayed in partly out of a sense of unfinished business, not to mention unrealized opportunity, explained Leslie North, VP of marketing for women's healthcare.

"If you look at the pregnancies in the United States today, 50% of them are unintended," she said. "And that means we still have a lot of work to do when it comes to contraception. When we look at some of the reasons why we have all of these unintended pregnancies, a lot of them just have to do with women saying 'there's not a method that's perfect for me.'"

"Our desire is to come up with products that fit individual customer needs so that eventually we get to a place where unintended pregnancies are a thing of the past," she continued.

### **Building On The Yaz Franchise**

On Sept. 24, FDA approved Bayer's Beyaz, an oral contraceptive that combines the hormonal ingredients in Yaz with 451 mcg of levomefolate calcium, a B vitamin. With the added folate, Bayer says Beyaz can provide the same contraceptive protection as Yaz while also guarding against neural tube defects (NTDs), brain or spinal birth defects such as spina bifida, if a pregnancy occurs.

Some observe that Beyaz shows only incremental differentiation from the highly popular Yaz. Bayer, however, argues otherwise: Labeling for Beyaz makes it the first contraceptive approved by FDA for four indications. In addition to folate's benefits in reducing risk of NTDs and the prevention of pregnancy, Beyaz, like Yaz, also is indicated for treatment of symptoms for premenstrual dysphoric disorder and treatment of moderate acne for women at least 14 years of age who have begun menstruation.

Bayer got Beyaz on U.S. shelves within two weeks of approval, North said, with about 35,000 pharmacies stocking the product.

Bayer did not detail its marketing plans for Beyaz, other than to say the effort will include both doctor- and consumer-focused components. The company plans to seek approval of Beyaz in Europe eventually, although it concedes a challenge there because the benefits of folate are not as broadly accepted as in the U.S.

While a contraceptive that also offers protection against potential birth defects may seem counterintuitive, Dr. Andrew Kaunitz, Associate Chair at the University of Florida-Jacksonville's Department of Obstetrics and Gynecology, says there is compelling logic behind such a product.

The key, Kaunitz noted, is that a pregnant woman can't start taking folate at the time of conception and get optimal protection against NTDs. His experience is that women 50 and over generally are compliant in including sufficient folate in their diets, but women of child-bearing age often are not.

HHS established a set of objectives around folates in 2000, explained North, including increasing folate levels in U.S. diets and increasing the number of pregnancies begun with a sufficient level of folate.



"Here we are in 2010 and they have not been able to achieve those objectives, which have now been transferred to [HHS'] Healthy Persons 2020 initiative," she said.

In the U.S., of the approximately 17 million women who use oral contraceptives, for various reasons there will be about 1 million pregnancies, added Richard Lynen, Bayer's Deputy Director of Medical Affairs for Women's Healthcare. Women also return to fertility very rapidly upon discontinuing oral contraception, making the presence of folate in a contraceptive potentially vital, he explained.

"So, if you look at that, it makes so much sense and [Beyaz is] a great option for women to be able to get their folate in a once-daily contraceptive that they're taking on a daily routine," North added, explaining what Bayer's marketing rationale will be.

### **Agile Hopes To Pick Up Ortho Evra Market**

While Bayer typifies the challenge for oral contraceptives to win market share through added value, privately held Agile hopes to prosper by offering a more convenient alternative to oral birth control with its once-weekly transdermal combination patch, AG200-15, currently in Phase III testing. The firm also recently got IND approval and began clinical testing of a progestin-only patch, AG900.

In 2002, J&J's Ortho McNeil division introduced a weekly patch, Ortho Evra, which quickly took significant market share away from oral contraceptives. However, due to safety concerns that its high level of estrogen presented risk for complications like blood clots, the product's market dwindled to \$115 million in 2009, making it just the fourth highest selling non-oral birth control option in the U.S. At its peak, Ortho Evra produced annual U.S. sales of around \$400 million, with an estimated one-quarter of women who used contraception trying the product.

Agile, whose product combines a lower level of estrogen along with levonorgestrel, which it calls the "gold standard" of progestins in terms of safety, seems ideally positioned because the company is led by Altomari, formerly VP of Ortho McNeil's Women's Health Care division, where he oversaw market preparations for Ortho Evra.

Executive chairman of Agile's board of directors, Altomari also succeeded Thomas Rossi as CEO on Oct. 18, with Rossi staying on as a scientific advisor. AG200-15 completed enrollment in its pivotal Phase III study, NEW CHOICE, in early October, putting the product two months ahead of schedule. Because of that development, Agile said it decided it needed to move into a "more commercial" orientation as it prepares to transition from a development company.

In Phase II, AG200-15 demonstrated that it delivered 60% less estrogen than Ortho Evra while meeting primary endpoints of ovulation suppression, cycle control and safety. The patch, which uses Agile's proprietary SkinFusion technology, also was well tolerated over seven days of use ("Agile's Low-Dose Birth Control Patch Heads For Phase III," "The Pink Sheet" DAILY, Sept. 2, 2008).

The potential benefits of a longer-acting contraceptive, such as a patch, are evident due to the failure rate of oral contraception, which frequently is due to the need for users to take the pill every day and often within the same three-hour time span, explained Kaunitz. While oral contraceptives have an annual failure rate of 1% to 2% in optimal conditions, actual practice finds a much higher pregnancy rate, he said.

"We know that in actual practice, the failure rate overall, including women of all age groups, is about 9%. And in very young women using the pill, for instance teenagers, the failure rate is in the double digits – it might be 15% or higher," Kaunitz said. "So one big trend is ... that longer-acting contraceptives are very important because women are human, many of them may not be great, consistent, day-to-day pill takers."

The SkinFusion technology combines skin-penetration enhancers – important because contraceptive hormones are difficult to deliver through the skin – with an adhesive system that makes the patch comfortable to wear and attractive, Rossi said in an interview.

Although Agile won't speculate on when it will file its NDA or hopes to launch the product, the Phase III trial began enrolling in August and requires subjects to use the patch for one year. In 2008, at the time Phase II data were released, the company said a 2011 filing was possible.



Having raised \$23.3 million in a Series F financing in May, Agile is preparing as if it will take AG200-15 to market itself, although the company and its investors are open to partnering and/or acquisition talks, Altomari said ("Agile Therapeutics Brings In \$23.3M Through Its Series F Round," Elsevier's Strategic Transactions Database, May 2010).

Altomari said he could envision a sales staff of between 100 and 350 reps, with a detailing focus on ob/gyns rather than general practitioners. "The ob/gyns are clearly the most prolific [prescription] writers of the product," he said. "The high-volume writers for contraceptives can outwrite by orders of magnitude the primary care audience. It's very dense on the upper deciles of ob/gyns. There's a fair amount of business in primary care but it tends to follow the thought leaders, in this case the ob/gyns."

#### **Another Approach: Adding Androgen**

In addition to Bayer and Agile, women's health-focused BioSante also is planning to make an entry into contraception with The-Pill-Plus, a Phase II oral contraceptive that combines androgen with estrogen and progestin to provide birth control while also addressing the loss of sexual desire faced by some women who use contraceptives.

"Paradoxically, women who take birth control pills actually have lower sexual desire and sexual activity than women of a similar age who do not take birth control pills," said BioSante CEO Stephen Simes. "Now, in a 22-year-old it doesn't matter. But when a woman gets to be 35 or 40 and her natural testosterone has declined and then you add the birth control, the levels of testosterone decline further."