F-D-C REPORTS —
FOUNDED 1939
$1,395 A YEAR

"The Pink Sheet"®

PRESCRIPTION PHARMACEUTICALS AND BIOTECHNOLOGY

THE NEWS THIS WEEK

Vol. 66, No. 7 February 16, 2004

Erbitux Clears FDA; Last Big Approval Of McClellan Era?

- **BRISTOL/IMCLONE EXPECT SECOND *ERBITUX* MANUFACTURING SITE APPROVAL** in July. Colorectal cancer treatment will be launched with product from Lonza Biologics facility. Approval is first step in Bristol's turnaround strategy **3**
- ***ERBITUX* SURVIVAL STUDY TO BE SUBMITTED TO FDA BY EARLY 2007, IMCLONE SAYS** following accelerated approval Feb. 12. Two 1,500-patient studies are expected to complete enrollment in second quarter 2005 and fourth quarter 2006. Erbitux review did not require advisory committee opinion, FDA says, because "the data stood on its own merits" **4**
- **FDA COMMISSIONER McCLELLAN MAY BE MOVING AGENCIES; CMS SPECULATION** indicates importance of Medicare Rx to Bush Administration. McClellan's background is perfect for CMS, though FDA post is viewed as more attractive **27**

Bayer/PPD Implitapide Development Follows *Zetia* Model As Statin Add-On

PPD will adopt Merck/Schering-Plough's ***Zetia*** model in developing Bayer's implitapide as an add-on therapy in the lipid-lowering market, PPD subsidiary MRL International CEO Evan Stein, MD/PhD, said.

"We're not looking to compete with the statin market." While "no new agent is going to replace statin therapy...we've seen ezetimibe, Zetia, come onto the market and obtain a significant market share," Stein said during PPD's investor day Feb. 5.

PPD is conducting *Phase II* proof-of-concept studies on the use of implitapide (BAY-13-9952) as an add-on to statin therapy. The contract research organization licensed the microsomal triglyceride transfer protein inhibitor from Bayer.

Implitapide could mark Bayer's return to the lipid-lowering market after the 2001 Baycol withdrawal.

PPD is hoping to demonstrate implitapide's safety and efficacy in homozygous and severe heterozygous familial hypercholesterolemia "where even high-dose statins are ineffective or inadequate," Stein said. The drug is also being studied for hypertriglyceridemia.

The studies, which will enroll approximately 200 patients, are expected to position the drug as a way to improve upon statin therapy, much in the same way that Zetia is marketed, Stein said.

"The addition here of another 18% to 24% [LDL reduction] would allow us to build on current therapy," he said. Zetia's success "provides an equal opportunity for other drugs that can produce 18% to 24% LDL reduction safely in a single-dose pill on top of all existing therapy."

When used as an add-on to a statin, Zetia has a statistically significant effect on reducing LDL cholesterol. For example, across all ***Lipitor*** (atorvastatin) doses the combination reduces LDL levels 56% versus 44% with the statin alone.

Some analysts have questioned the pace of Zetia's uptake, however; new and total prescription share in December was 5.2% and 4.9%, after a little over a year on the market ("The Pink Sheet" Feb. 2, 2004, p. 11).

Patients initially targeted for implitapide therapy will likely be the 5%-7% of high cholesterol patients that are statin-intolerant and the 10% -15% who are at high risk for cardiovascular disease and have not reached their LDL goals, Stein indicated.

Zetia is similarly targeted. By contrast, Merck expects the ***Zetia/Zocor*** fixed-dose combination pending at FDA to compete directly with single-agent statins for patients who are diagnosed with high cholesterol but not treated ("The Pink Sheet" Dec. 22, 2003, p. 23).

PPD suggested implitapide could eventually be used as a triple combination therapy with Zetia and a statin. In that case, Stein estimated that LDL-cholesterol reductions could range between 66%-72%.

PPD expects Bayer will be interested in buying back rights to implitapide after seeing the *Phase II* results. "If they meet, I think, even a reasonable hurdle, Bayer will be pretty keen to take it," Stein maintained.

Bayer will have the opportunity to relicense implitapide from PPD by reimbursing *Phase II* costs and establishing milestone and royalty payments.

"One of the things that may drive them is if they don't take it, they know a number of other major pharma would probably. They are speaking to us and are interested in the results," Stein said.

Implitapide would mark Bayer's return to the lipid-lowering market; the company withdrew the statin ***Baycol*** (cerivastatin) in 2001 due to reports of rhabdomyolysis, including deaths ("The Pink Sheet" Aug. 13, 2001, p. 4).

While Stein acknowledged that MTP inhibitor projects have been pursued by a number of companies, including Bristol-Myers Squibb, Johnson & Johnson and Pfizer, he argued that the toxicity seen with some of those projects was related to the high doses used during trials

"None of them were looking at LDL reductions or cholesterol reductions" as low as the 20% range, he said. "They didn't consider that viable in terms of marketing. There was no Zetia on the market, so there was no model for them."

PPD is conducting three 39-week *Phase II* studies with dose titration occurring every five weeks based on safety and tolerability examined at four weeks. The starting dose will be 10 mg daily, escalating by 5 mg/day every five weeks to a maximum 40 mg/day. ♦♦