

02 | GlaxoSmithKline

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HEADCOUNT	100,000
YEAR ESTABLISHED	2000
PHARMA REVENUES	\$37,003 +9%
TOTAL REVENUES	\$42,803 +9%
NET INCOME	\$8,210 +35%
R&D BUDGET	\$6,371 +12%

DRUGS APPROVED/LAUNCHED

<i>Drug</i>	<i>Indication</i>
coreg CR	hypertension and CHF – daily
altabax/altargo	bacterial skin infections
relenza	influenza prophylaxis
trexima	migraine – fixed dose combination
hycamtin	cervical cancer, second-line therapy
seretide	asthma – initial maintenance therapy
priorix-tetra	measles, mumps, rubella and varicella prophylaxis
flulaval	influenza prophylaxis
veramyst	seasonal and year-round allergy symptoms
tykerb	advanced or metastatic breast cancer (HER-2)
cervarix	prevention of cervical cancer and precancerous lesions (Australia)
seretide/advair	bronchial asthma (Japan)
arixtra	venous thromboembolic events

DRUGS CANCELLED

<i>Drug</i>	<i>Indication</i>
redona	diabetes
brecanavir	HIV

DRUGS PENDING APPROVAL

<i>Drug</i>	<i>Indication</i>
arixtra	acute coronary syndrome (approvable)
entereg/entrareg	post operative ileus (approvable)
ariflo	COPD (approvable)
lamictal XR	epilepsy – partial seizures, once-daily
requip extended release	restless legs syndrome
requip modutab/ XL 24 hour	Parkinson's disease – once-daily controlled release
tykerb	refractory breast cancer
avamys/allermist	allergic rhinitis
seretide/advair	COPD – mortality claim
rotarix	rotavirus induced gastroenteritis prophylaxis
daronix	pandemic influenza prophylaxis
flu pre-pandemic	pandemic influenza prophylaxis
cervarix	human papilloma virus infection prophylaxis
globorix	diphtheria, tetanus, pertussis, hepatitis B, Haemophilus, influenzae type b disease, Neisseria meningitis groups, A & C disease
DTaP-IPV	pediatric booster vaccine for immunization against diphtheria, tetanus, whooping cough (pertussis), and polio
hycamtin	relapsed small cell lung cancer

DRUGS IN PHASE IIB AND BEYOND

<i>Drug</i>	<i>Indication</i>
hycamtin	ovarian cancer - first-line therapy, small cell lung cancer, second-line therapy
pazopanib	renal cell cancer
promacta	long-term and short-term idiopathic thrombocytopenic purpura
tykerb	breast cancer, head and neck squamous cell carcinomas
darapladib	atherosclerosis
ambrisentan	pulmonary arterial hypertension
avodart	reduction in the risk of prostate cancer
belimumab	systemic lupus erythematosus
entereg/entrareg	opioid induced bowel dysfunction
mepolizumab	hypereosinophilic syndrome, severe asthma and nasal polyposis

DRUGS COMING OFF PATENT

<i>Drug</i>	<i>Indication</i>
zofran	oncology (2006)
coreg	heart disease (2007)
paxil/seroxat	CNS (2006-EU, 2007-U.S.)
requip	CNS (2007-U.S., 2008-EU)
serevent	respiratory (2008)

TOP SELLING DRUGS

<i>Drug</i>	<i>Indication</i>	<i>\$</i>	<i>(+/- %)</i>
seretide/advair	asthma, COPD	\$6,106	12%
avandia/avandamet	diabetes	\$3,032	25%
lamictal	epilepsy, bipolar disorder	\$1,836	19%
wellbutrin	depression	\$1,659	23%
zofran	oncology, emesis	\$1,561	2%
valtrex	herpes	\$1,557	23%
coreg	heart disease	\$1,436	38%
imitrex	CNS	\$1,310	3%
flovent	respiratory	\$1,215	5%
paxil	CNS	\$1,143	2%
augmentin	antibacterial	\$1,050	-13%
combivir	antiviral	\$973	-8%
flonase	respiratory	\$573	-52%
serevent	respiratory	\$536	-11%
trizivir	antiviral	\$494	-10%
requip	restless legs	\$494	74%

Account for 67% of total pharma sales, down from 68% in 2005.

GLAXOSMITHKLINE BARELY FELL BEHIND Sanofi-Aventis in last year's rankings (notwithstanding my bone-headed typo in SA's revenues), but GSK left no doubts as to its #2 status this year, passing SA by almost \$1.5 billion in pharma revenues and nearly doubling SA's rate of growth. Unfortunately, one of the biggest reasons for GSK's jump may have turned into one of its biggest risks.

In May 2007, the New England Journal of Medicine published a paper analyzing data from 42 separate trials of GSK's diabetes drug Avandia. The author of the paper, Dr. Steve Nissen of the Cleveland Clinic, concluded that Avandia increased heart attack risk by 43% and heart death risk by 64%.

There were plenty of critics of Dr. Nissen's approach — compiling data from varied trials and lumping 28,000 patients into one meta-pool — but the FDA chose to err on the side of caution (if they erred) by issuing a safety warning for Avandia. The immediate effect on GSK was near-Vioxx-level, with new prescriptions of Avandia dropping to zero and the company losing \$15 billion in market cap. There's no official word on how far Avandia sales have fallen, but the "black box" label warning that the FDA requested for Avandia (and competitor Actos) will definitely hurt the company's performance in 2007. (Results from 2Q2007 will tell part of the story, and they should be available a week or so after this issue.)

GSK has defended Avandia's safety profile and noted that it's in the midst of a large, long-term trial to ascertain CV out-

comes in diabetics. The independent monitoring board of that trial cleared it to continue after reviewing interim data. In the meantime, Merck's Januvia looks to be a major beneficiary of the scare. And GSK is facing its first suit from the family of a man who died while he was taking Avandia.

Patents Ending

GSK has more going on than Avandia. After all, it's "only" a \$3 billion franchise, making it less than half the size of the Seretide/Advair juggernaut, which posted \$6.1 billion in 2006 sales. Advair faces a direct challenger in AstraZeneca's Symbicort asthma inhaler, approved in June 2007, but its U.S. head start over Symbicort looks insurmountable (I know: famous last words). While AZ has touted Symbicort's quicker onset, neither drug is intended for fast relief, but rather long-term maintenance treatment.

It may sound like I root against big companies, but it's only because I don't believe that companies in any industry can sustain growth once they reach a certain size; it's just a law of maturation. One school of thought says that the bigger companies can afford to nurture a smaller product until it reaches blockbuster status, but another school says that bigger companies can only develop potential blockbusters as defined by their marketing departments.

As we did for Pfizer, let's check out the expiration dates that GSK stated for its top sellers:

Seretide/Advair	2010	Flovent	2011
Avandia/Avandamet	2012	Paxil	2007
Lamictal	2009	Augmentin	expired
Wellbutrin	expired	Combivir	2012
Zofran	2006	Flonase	expired
Valtrex	2009	Serevent	2008
Coreg	2007	Trizivir	2016
Imitrex	2009	Requip	2007

Most of these dates are for "classic" versions a drug, not the various CR, IR, XXL and other versions. Still, it paints a bleak picture when the big seller with the longest patent protection has been slapped with a "black box" warning. Nearly every other major contributor will be under assault by 2010.

The company has a number of great prospects in its pipeline, but I just don't think they're going to replace lost sales quickly enough in the three- to five-year range to overcome generic erosion. In 1Q2007, sales of Wellbutrin XL, Zofran and Flonase dropped 37%, 60% and 49%, respectively. Overall, pharma sales rose only 3% in the quarter, and we can be sure 2Q will be a hash because of the Avandia crisis.

Cancer Growth

Although GSK is spread across nine major therapeutic fields, oncology looks like the area of biggest immediate potential. In March 2007, the company received approval for Tykerb, a breast cancer treatment presently positioned as an alternative to Herceptin (if that treatment fails). At a June 2007 analysts meeting, the company declared its plans to bring five more oncology compounds to the market between 2007 and 2010.

At the announcement, Moncef Slaoui, GSK's chairman of

THE LOWE DOWN

GSK SEEMED UNTIL RECENTLY TO BE living the best approximation our industry offers to a charmed life. The row over Avandia's cardiac effects — if it has cardiac effects — put an end to that, though. (Welcome to the club, folks — we knew you'd show up eventually, and we kept a table open for you). Still, whenever people start to say nasty things about big drug company mergers, someone usually ends up pointing out that "Well, Glaxo and SmithKline worked out, anyway."

They may well have. If so, it's probably (to an outside observer) because they've been willing to spend quite a bit of money on quite a bit of science. Laying out for science is no guarantee, of course, as GSK's nuclear receptor effort points out, but not spending money on it is a guarantee in the opposite direction. All things considered, it's probably better to open up the treasury a bit, rather than use a merger as an excuse to put down even bigger bets on the same projects as before.

The company will need to keep doing that to break into some of the markets that they aren't traditional powers in (like oncology). How they weather the Avandia storm this year will tell us a lot.

—Derek Lowe

R&D, said, "We are actively developing late-stage medicines in over 12 different cancer types, from pioneering treatments such as Tykerb to vaccines that can treat as well as prevent cancer. Moving deeper into the pipeline we believe that this productivity in oncology can be sustained as we have a significant number of promising new compounds in early-stage discovery."

Cervarix is chief among the next wave of GSK onco-compounds. A vaccine against human papillomavirus (HPV), the main cause of cervical cancer, Cervarix's U.S. filing was delayed until March 2007 to gather more clinical data. With no priority status for its filing, GSK doesn't expect to launch Cervarix until 2008 (it was approved in Australia in May 2007).

The vaccine will be playing catch-up with Merck's Gardasil, but rather than treat their competition like a foot-race, GSK has elected to make it a boxing match. The company is conducting head-to-head trials of the two vaccines to determine which one generates the greater immune response. It's an intriguing (desperate?) approach for GSK, which needs to do something to capture a share of a market that may reach \$4 billion annually.

Vaccinate

As with many other companies at the top of this list, vaccines have become an important part of the business for GSK. The vaccines unit brought in more than \$3.0 billion in sales last year

ACQUISITIONS

Target: Praecis Pharmaceuticals

Price: \$54.8 million

Announced: December 2006

What they said: "Praecis has created novel therapeutic programs and innovative chemical-synthesis and screening technology that will complement our own discovery capabilities."

—Allen Oliff, senior vice president,
Molecular Discovery Research, GSK

Target: Domantis Ltd.

Price: \$454 million

Announced: December 2006

What they said: "Domantis has pioneered the extension of antibody therapies to potentially far wider applications than has been possible with conventional MAbs."

—Mike Owen, senior vice president,
Biopharmaceuticals CEDD, GSK

(+23%), driven mainly by its infant and hepatitis vaccines. FluLaval, part of the September 2005 ID Biomedical acquisition, brought in nearly \$500 million in its first full year.

The company invested more than \$600 million in its vaccine facility in St. Amand-les-Eaux, France, to boost production in formulation, fill/finish and packaging, and also spent \$300 million on primary manufacturing sites in Singapore and Hungary, enhancing its capacities in Asia and Europe.

Bio-Push

GSK also kept up with its neighbors by enhancing its biopharmaceuticals program. The acquisition of Domantis at the end of 2006 may slingshot GSK past some of its competitors if Domantis' lead technology, domain antibodies (dAbs), pan out. It's still a nascent platform (as in 5 to 10 years till there's anything to show for it), but dAbs, which contain antibody fragments, are supposed to be orally dosable, and that would change the shape of the drug industry as we know it.

The company's bio-strategy also includes in-licensing compounds, of course. In December 2006, GSK made a big splash by paying \$100 million in licensing fees and buying \$357 million in stock from Genmab to co-develop HuMax-CD20, which is in Phase III testing to treat B-cell chronic lymphocytic leukemia (B-CLL) and follicular non-Hodgkin's lymphoma (NHL) and in Phase II for rheumatoid arthritis. It belongs to the same class as Genentech and Biogen Idec's Rituxan, but is a fully human MAb. Not including royalties, payments could reach as high as \$2.1 billion, which GSK would be happy to pay if it had a chunk of Rituxan's market. And that would certainly jump-start GSK's oncology business.

If Cervarix can prove its mettle against Gardasil, and the Avandia studies disprove Dr. Nissen's meta-analysis, GSK could find itself in good position to weather the generic storm in the years ahead. ■