

TOP 10 BIOPHARMA



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HEADCOUNT	11,000
YEAR ESTABLISHED	1976
BIOPHARMA REVENUES	\$9,443 +24%
ROYALTY REVENUES	\$1,984 +26%
TOTAL REVENUES	\$11,724 +47%
NET INCOME	\$2,769 +31%
R&D BUDGET	\$2,446 +38%

DRUGS PENDING APPROVAL

<i>Drug</i>	<i>Indication</i>
avastin	first-line metastatic renal cell carcinoma, relapsed glioblastoma multiforme
rituxan	rheumatoid arthritis DMARD-inadequate responders
herceptin	adjuvant HER2-positive breast cancer

DRUGS IN PHASE IIB AND BEYOND

<i>Drug</i>	<i>Indication</i>
2nd gen. anti-CD20	lupus nephritis, rheumatoid arthritis
avastin	diffuse large B-cell lymphoma, GIST, high risk carcinoid, hormone refractory prostate cancer, metastatic head and neck cancer, relapsed platinum-sensitive ovarian cancer
avastin +/- tarceva	first-line metastatic, non-squamous, NSCLC, second-line metastatic NSCLC
herceptin	adjuvant HER2-positive breast cancer
lucentis	diabetic macular edema, retinal vein occlusion
pertuzumab	first-line HER2-positive metastatic breast cancer
rituxan	follicular NHL, relapsed chronic lymphocytic leukemia
rituxan	active rheumatoid arthritis, ANCA-associated vasculitis, lupus nephritis
tarceva	adjuvant NSCLC, first-line metastatic NSCLC
TNKase	central venous access device occlusion, hemodialysis catheter clearance
xolair	pediatric asthma

EARLY RESEARCH PROJECTS

<i>Drug</i>	<i>Indication</i>
3rd gen. anti-CD20	chronic lymphocytic leukemia, NHL
abt-263	chronic lymphocytic leukemia, lymphoid malignancies
anti-abeta	Alzheimer's disease
anti-CD4	autoimmune disease
anti-CD40	diffuse large B-cell lymphoma, multiple myeloma, NHL
anti-IL13	asthma
anti-oxLDL	secondary prevention of cardiovascular events
huMAb ox40L	asthma
iap antagonist	cancer
mek inhibitor	cancer
metmab	cancer
pi3 kinase inhibitor	cancer
rhuMAb Beta7	ulcerative colitis
rhuMAb IFNalpha	systemic lupus erythematosus

TOP SELLING DRUGS

<i>Drug</i>	<i>Indication</i>	<i>\$</i>	<i>(+/- %)</i>
Avastin	colorectal cancer	\$2,296	32%
Rituxan	lymphoma, rheumatoid arthritis	\$2,285	10%
Herceptin	breast cancer	\$1,287	4%
Xolair	asthma	\$472	11%
Tarceva	lung cancer	\$417	4%
Lucentis	wet age-related macular degeneration	\$815	114%
Nutropin/Protropin	growth hormone	\$371	-2%

Account for 84% of total pharma sales, down from 87% in 2006.

WITH AMGEN IN THE DOLDRUMS, is Genentech in position to close the gap? Not exactly. The perennial #2 on our list posted great numbers for 2007, but growth slowed in 1Q08 as a key product ran into some unique difficulties.

In last year's profile, I explained how Lucentis, Genentech's treatment for wet age-related macular degeneration (AMD), was facing competition from its own precursor, Avastin. It seems doctors were willing to use repackaged Avastin as a replacement for Lucentis, saving about \$1,960 per \$2,000 dose of Lucentis. Genentech blew a gasket when this practice came up, and tried to restrict Avastin sales from

compounding pharmacies, which were doing the actual repackaging.

In December 2007, Genentech reached a compromise with two ophthalmologists' societies; they were allowed to order Avastin themselves and have it delivered to compounding pharmacies, but the pharmacies themselves could no longer order it. Lucentis sales were \$815 million in its first full year, but 1Q08 numbers dipped from \$211 million to \$198 million, hurt by Avastin substitutions. If that \$800 million range turns out to be the peak for Lucentis, Genentech's going to be one unhappy company.

TOP 10 BIOPHARMA: Genentech

Glassy Eyed

There's a side story about Genentech's restrictions on switching Avastin for Lucentis. In that version, the FDA inspected Genentech's Avastin manufacturing site and questioned the safety of the drug's preparation in ocular use. According to the company, it increased its visual inspection standards and determined that four lots were not suitable for use in the eye (but were just fine for anticancer indications). Because of this failure to meet standards for an off-label use it doesn't approve of, Genentech said it destroyed 350,000 vials of Avastin with a market price in excess of \$200 million.

According to Jacob Goldstein at the *Wall Street Journal's* Health Blog, FDA called shenanigans on that claim, and declared that the lots would not have been suitable in any indications, including oncology, because of microscopic levels of glass found in the vials. The implication is that those lots of Avastin were flat-out defective, and the company used the controversy over the Lucentis switch to justify destroying the lots. Genentech disagreed with that assessment.

Yarr! Avastin, Matey!

If there's an upside to this, it's that the switch contributed a little to Avastin revenues, were up 32% in 2007. That growth rate made Avastin Genentech's top performer last year, squeaking past Rituxan.

April turned out to be the cruelest month for Rituxan trials. In April 2008, Genentech and partner Biogen Idec announced that Rituxan had failed trials in both primary progressive multiple sclerosis (PPMS) and Lupus. On Ed Silverman's excellent blog *Pharmalot* (www.pharmalot.com), he ran the following assessment of Avastin's two April failures, courtesy of Jim

Reddoch, a biotech analyst with Friedman, Billings & Ramsey:

"The negative result has implications beyond Rituxan. Genentech has been developing a second-generation anti-CD20 antibody (same mechanism as Rituxan, currently in Phase III for RA and Phase II for MS). This drug is being developed as a more benign version of Rituxan for use in patients with non-life-threatening conditions, including the autoimmune diseases.

"The fact that Rituxan, the more potent drug, was unable to meet a single endpoint in this trial, and failed in PPMS, does not instill confidence in the prospects for the next-generation version. This removes another potential growth area from a company that is in dire need of them, as the company's other drivers are slowing."

The Avastin news hasn't been all bad. In February, the FDA approved Avastin with Paclitaxel chemotherapy for first-line treatment of breast cancer. The approval was a bit surprising,

PARTNER UP!

AS LAST YEAR'S ISSUE went to press (or thereabouts), Genentech signed a development agreement with Abbott Laboratories. Interestingly, the two Abbott compounds in the agreement are small molecule anti-cancer agents, one of which is a VEGF blocker, just like Avastin. Terms of the deal weren't disclosed, but some analysts wondered if the deal may be a hedge against an Avastin slowdown. Since both compounds are just finishing Phase I, that's a pretty long-term hedge.

This June (2008, that is), Genentech signed a development agreement with Symphogen. Symphogen will apply its Symplex antibody discovery technology platform to identify novel infectious disease drug candidates. Genentech will gain access to the company's Sympress technology to produce recombinant polyclonal antibodies. Genentech will obtain an exclusive worldwide license to candidates developed through this agreement and will fund associated R&D costs. The deal's full value could pass \$330 million plus royalties. Curiously, Genentech has made no comment or press release about this collaboration.

THE LOWE DOWN

GENENTECH USED TO BE "one of the" biggest and most powerful biotech companies — but Avastin's success and Amgen's recent problems are beginning to remove all the qualifying phrases. The company keeps throwing around numbers in the dozens for the drugs that they're advancing to the clinic in the next few years, which makes you wonder where they're going to find all the clinicians (and all the patients). But gather ye rosebuds while ye may: this is the time to do it, when the money is rolling in, and hope that the hit rate will be high enough to keep the party going.

A strong development pipeline can only help them out when that biogeneric revolution does get around to occurring. Biotech companies will then have to live off their wits, like their small-molecule brethren, with patent expirations ticking away in the background the whole time. From the look of it, Genentech is doing a better job than some of preparing for that particular asteroid.

—Derek Lowe

since a December 2007 advisory committee meeting recommended against the new indication, 5-4. Analysts believe that the new indication will lead to another bump in Avastin sales, but they also note that the drug will face greater competition from ImClone's Erbitux, which will seek expansions into first-line head and neck cancer approval in mid-2008, lung cancer in 4Q08 and colon cancer in 1Q09.

Genentech's runner-up status in our Top 10 list looks secure for another year, but any hope of climbing to #1 on our list are pipe(line) dreams. ■