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BIOWORLD®

TOP 25 BIOTECHNOLOGY DRUGS REPORT

1. RITUXAN

RITUXAN

Proper name: Rituximab
Type: Anticancer, anti-inflammatory
Drug Developer: Genentech Inc.
Location: South San Francisco, California
Website: www.gene.com
Indication(s): For the treatment of relapsed or refractory low-grade or follicular B-cell non-Hodgkin's lymphoma (NHL), slow-growing NHL, aggressive NHL in combination with the chemotherapy drugs cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP), to diffuse large B-cell lymphoma in combination with CHOP or other chemotherapy regimens, and in combination with methotrexate (MTX) for rheumatoid arthritis
Approval Date: November 1997
Total 2007 Revenue (Reported by Roche): $5.467 billion
2007 Revenue Reported by Genentech: $2.285 billion
2007 Revenue Reported by Biogen Idec: $926 million
Percentage of Roche's Total Revenue: 12.47 percent
Percentage of Genentech's Total Revenue: 19.49 percent
Percentage of Biogen Idec's Total Revenue: 29.19 percent

Indications and Statistics

The U.S. government is seeking to eliminate not only lymphoma, but all cancer within the next decade, through an agenda of the National Cancer Institute (NCI) titled The 2015 Challenge. The optimistic and aggressive agenda includes an objective to support interventions that reduce the adverse effects of cancer treatments, much like what Rituxan is indicated to do. Such a commitment by an agency as prominent as the NCI could bode well for Rituxan's class of drugs and augment its already successful franchise with an infusion of patients and revenue.

There are five kinds of Hodgkin's lymphoma (also known as Hodgkin's disease). Non-Hodgkin's lymphoma (NHL) has even more categories, with more than 25 forms of the cancer. More than 63,000 new cases of NHL developed in 2007, with approximately 18,893 people dying each year in the U.S. from the disease. Non-Hodgkin's lymphoma is slightly more prevalent in men than in women, and Caucasians are more often affected than African-Americans or Asian-Americans. More than 90 percent of non-Hodgkin's lymphoma cases occur in adults.

History of Rituxan

Rituxan is a biotechnology therapeutics heavyweight that is excelling in fighting to extend its relevance, as it encounters R&D obstacles in secondary indication trials and looming biogeneric competition in the near future. The drug improved its revenue by 29 percent in 2007, increasing from $3.881 billion in 2006 to $5.467 billion in 2007. Rituxan has established a list of "Firsts" in its 12-year market run:

- First FDA-approved therapeutic antibody to treat cancer.

· First biologic therapy for the treatment of relapsed or refractory, low-grade or follicular, CD20-positive, B-cell NHL.

· First and only biologic therapy in combination with CVP chemotherapy that improves PFS (survival until disease progression or death) in patients with first-line follicular, CD20-postive, B-cell NHL.

· First treatment of any kind (with CHOP or anthracycline chemotherapy) to have improved OS in first-line CD20-positive, DLBCL in more than 25 years.

· First and only biologic therapy to improve PFS, with CHOP or anthracycline chemotherapy, in first-line CD20-positive, DLBCL.

Rituxan's next "first" may be less welcomed by its makers, inasmuch as the drug may be among the first round of biotechnology therapeutics to be vulnerable to biogenerics. Rituxan's venerability also stands to expose it to the initial round of biosimilars competition, if the 12-year period of brand exclusivity that is currently being considered in congressional debate regarding the specifics of biogenerics legislation is designated as the standard.

The research and development program for Rituxan was initiated in 1979, when Lee M. Nadler, an oncologist and hematologist at Dana-Farber Cancer Institute, developed a monoclonal antibody (MAb) that bound to CD20. CD20 is an antigen that is expressed on both normal and malignant human B cells, which are cells that produce antibodies. Rituxan is a related MAb that was developed by researchers at Idec Pharmaceuticals Inc. (now Biogen Idec Inc.). The therapeutic antibody drug, according to Genentech, binds to the CD20 antigen on the surface of normal and malignant B-cells in order to enlist the body's natural defenses to attack and kill the marked B-cells. Stem cells (B-cell progenitors) in bone marrow lack the CD20 antigen, allowing healthy B-cells to regenerate after treatment and return to normal levels within several months.

Rituxan first received approval from the FDA in November 1997 for the treatment of relapsed or refractory low-grade or follicular B-cell non-Hodgkin's lymphoma. A year later, it was approved for the treatment of slow-growing NHL that had either relapsed or not responded to initial treatment. Rituxan was approved for the treatment of aggressive NHL in combination with the chemotherapy drugs cyclophosphamide, doxorubicin, vincristine and prednisone in 2002. The drug was approved for the treatment of rheumatoid arthritis three years later. In Europe, it was first approved in 1998 as MabThera. According to data submitted to BioWorld by Biogen Idec and without consideration to pending U.S. biosimilars legislation, Rituxan's U.S. patent will expire between 2015 and 2018, and in the rest of the world, in 2013, subject to potential patent term extensions.

The CD20 antigen that the drug targets is present in more than 90 percent of NHLs. Like Remicade, Rituxan is a chimeric monoclonal antibody, meaning that it uses both human and mouse components. It sells for about $18,000 per year wholesale, per patient.

The completion of Genentech's $2.1 billion merger with Roche Holding Ltd. in 1990 resulted in Genentech's heavily committed financial support for Rituxan's development, and Genentech now owns about 70 percent of the drug in addition to sharing U.S. promotional and continued development responsibilities with Biogen Idec. Genentech reported in its 2007 annual report that its revenue

from Rituxan increased from $2.075 billion in 2006 to $2.285 billion in 2007.

The drug is marketed outside of the U.S. by F. Hoffmann-La Roche Ltd. Zenyaku Kogyo Co. Ltd. and Roche co-promote the product in Japan. With Roche reporting worldwide MabThera/Rituxan sales of $5.467 billion in 2007, it is its top-selling drug.

New Approvals and Current Trials

Rituxan obtained several supplementary indication approvals in 2006, but has been unsuccessful in its latest endeavors to gain additional approvals.

In 2006, it was approved for rheumatoid arthritis in the U.S., EU and Switzerland; for the first-line treatment of diffuse large B-cell CD20-positive NHL in the U.S.; for the first-line treatment of patients with follicular NHL in combination with cyclophosphamide, vincristine and prednisone (CVP) chemotherapy in the U.S.; for maintenance therapy for patients with relapsed or refractory follicular NHL in the EU and Switzerland; and for the treatment of low-grade NHL following first-line treatment with CVP chemotherapy in the U.S.

Phase II/III trials of Rituxan for primary progressive multiple sclerosis (MS) and systemic lupus erythematosus (SLE) for the drug have not fared so well. The companies announced in April 2008 that the lupus trial did not meet any of its stated objectives and that Rituxan increased the rate of herpes infection and neutropenia (low white blood count) in patients.

The companies said there have been two reports of progressive multifocal leukoencephalopathy (PML) in Rituxan-treated patients with SLE. The condition itself may predispose patients to PML, and a causal relationship between Rituxan and PML has not been established but cannot be ruled out, the companies said.

That negative news regarding the lupus indication came right on the heels of results announced one week earlier showing that Rituxan's Phase II/III clinical trial to treat primary-progressive multiple sclerosis (PPMS) failed, while experiencing a rate of 16.4 percent serious adverse events, compared with 13.6 percent for the clinical trial's placebo. PPMS is the most severe form of MS and there are currently no approved drugs for the indication.

Rituxan didn't significantly slow down the advancement of PPMS, which progressively compromises motor function, induces tremors, causes tingling and triggers fatigue. Secondary results, such as whether Rituxan improved MRI scans of patients' brains, were not released.

Rituxan is also undergoing Phase III clinical trials for Disease Modifying Anti-Rheumatic Drug (DMARD) for inadequately responding rheumatoid arthritis patients, antineutrophil cytoplasmic antibodies-associated vasculitis and lupus nephritis.

No new drugs have been approved to treat lupus for decades, and it is treated by immune-suppressing agents that have serious side effects.

Genentech and Biogen are conducting separate clinical trials assessing Rituxan's effectiveness against

lupus nephritis, a common lupus complication in which the disease attacks the kidney. The results of those trials are expected in 2009, but a successful result and that indication expansion could give Genentech and Biogen Idec as much as $1 billion in additional annual Rituxan revenue.

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25. KOGENATE

KOGENATE

Proper name: Recombinant Factor VIII
Type: Antihemophilic
Developer: Bayer HealthCare AG
Location: Pittsburgh, Pennsylvania
Web address: www.bayerhealthcare.com
Indication(s): To treat or prevent bleeding in patients with hemophilia A
Approval Date: February 1993; Kogenate FS approved in June 2000
2007 Revenue: $1.262 billion
Percentage of Bayer's Total Revenue: 2.45 percent

About Kogenate

Bayer introduced its first Factor VIII in the early 1970s, and in February 1993, Bayer company Miles Inc. received approval for Kogenate. Genentech Inc. of South San Francisco, Calif., originally cloned the Factor VIII gene and licensed it to Miles in 1984 as part of a collaborative agreement.

It was the second genetically engineered Factor VIII product to win FDA approval. The first, Recombinate, was developed by Baxter Healthcare Corp.'s Hyland Division and Genetics Institute Inc. of Cambridge, Mass., in a long-standing collaboration. FDA approved Recombinate in December 1992.

In June 2000, Bayer Corp., of Pittsburgh, said the FDA approved Kogenate FS Antihemophilic Factor (recombinant), formulated with sucrose. Kogenate FS has a higher concentration and smaller fluid volume than Kogenate, which reduces intravenous infusion time.

In March 2008, Bayer announced that it had received a complaint jointly filed in the U.S. by Novartis Vaccines and Diagnostics Inc. and Novo Nordisc A/S. Those companies allege that Kogenate's production and distribution infringes a patent issued in 2006. Bayer has said that it will "vigorously defend itself against the complaint."

About Hemophilia

Hemophilia A is caused by a lack of factor VIII, which is a naturally occurring protein that helps blood to clot. The Kogenate FS molecule is a large recombinant protein, and it functions much like naturally occurring Factor VIII. The drug is prepared using recombinant DNA technology. When Kogenate FS is injected, it works by helping to stop bleeding and to close wounds.

An estimated 17,000 Americans have hemophilia. The most common form, hemophilia A, also is called classic hemophilia. In this form of the disease, Factor VIII is malfunctioning or undersupplied. Hemophilia B occurs when Factor IX is malfunctioning or undersupplied.

About Bayer HealthCare

Bayer HealthCare AG is a subsidiary of Bayer AG. Its Pharmaceuticals Division, which comprises the

former Biological Products division, has three business units: Oncology, Hematology/Cardiology and Primary Care.

Sales in the Hematology/Cardiology business unit fell by 9.5 percent in 2007. Kogenate sales, however, increased by 7.7 percent, in part due to an expanded registration in the European Union it received in January 2007.

Money Raised By Biotech, 2000-2007 (in billions of U.S. dollars)

	Public/ Other	Private Biotechs	Public Offerings
2000	10.09	3.94	23.64
2001	6.12	3.75	4.49
2002	5.33	3.23	1.39
2003	9.46	3.33	3.63
2004	10.46	4.89	5.46
2005	9.73	4.81	5.58
2006	8.53	5.13	6.63
2007	13.42	6.23	5.13

SOURCE: *BioWorld Financial Watch.*

Top Biotech Companies by 2007 Revenue

Amgen Inc.	$14,771M
Genentech Inc.	$11,724M
Gilead Sciences Inc.	$4,230M
Genzyme Corp.	$3,814M
Biogen Idec Inc.	$3,172M
Cephalon Inc.	$1,773M
Celgene Corp.	$1,406M
ImClone Systems Inc.	$591M
Affymetrix Inc.	$371M
PDL BioPharma Inc.	$259M
Albany Molecular Research Inc.	$193M
QLT Inc.	$128M
AEterna Zentaris Inc.	$42M

SOURCE: *BioScan: The Worldwide Biotech Industry Reporting Service.*

Top Biotech Research Tools/Services Companies by 2007 Revenue

Thermo Fisher Scientific Inc.	$9,746M
Applied Biosystems Group	$2,093M
Sigma-Aldrich Corp.	$2,039M
bioMerieux SA	$1,691M
Millipore Corp.	$1,53M
Pharmaceutical Product Development Inc.	$1,414M
Invitrogen Corp.	$1,282M
Idexx Laboratories Inc.	$923M
Qiagen NV	$650M
Bruker Corp.	$548M
Gen-Probe Inc.	$403M
Affymetrix Inc.	$371M

SOURCE: *BioScan: The Worldwide Biotech Industry Reporting Service.*

10 Leading Causes of Death by Broad Income Group

High-income countries	Deaths in millions	% of deaths
Coronary heart disease	1.34	17.1
Stroke and other cerebrovascular diseases	0.77	9.8
Trachea, bronchus, lung cancers	0.46	5.8
Lower respiratory infections	0.34	4.3
Chronic obstructive pulmonary disease	0.3	3.9
Colon and rectum cancers	0.26	3.3
Alzheimer's and other dementias	0.22	2.7
Diabetes mellitus	0.22	2.7
Breast cancer	0.15	1.9
Stomach cancer	0.14	1.8

Middle-income countries	Deaths in millions	% of deaths
Stroke and other cerebrovascular diseases	3.02	14.6
Coronary heart disease	2.77	13.4
Chronic obstructive pulmonary disease	1.57	7.6
Lower respiratory infection	0.69	3.3
HIV/AIDS	0.62	3
Perinatal conditions	0.6	2.9
Stomach cancer	0.58	2.8
Trachea, bronchus and lung cancer	0.57	2.7
Road traffic accidents	0.55	2.6
Hypertensive heart disease	0.54	2.6

Low-income countries	Deaths in millions	% of deaths
Coronary heart disease	3.1	10.8
Lower respiratory infections	2.86	10
HIV/AIDS	2.14	7.5
Perinatal conditions	1.83	6.4
Stroke and other cerebrovascular diseases	1.72	6
Diarrhoeal diseases	1.54	5.4
Malaria	1.24	4.4
Tuberculosis	1.1	3.8
Chronic obstructive pulmonary disease	0.88	3.1
Road traffic accidents	0.53	1.9

SOURCE: World Health Organization.

Year-End Financial Data for Top 25 Drug Developers

All figures are in U.S. dollars unless otherwise indicated.

Abbott Laboratories

*health care company

	YE 2007	YE 2006
Revenue	$25.914B	$22.476B
Net income	$3.606B	$1.717B
Earnings per share	$2.31/share	$1.12/share
Average shares outstanding	1.560B	1.537B
Total assets	$39.714B	$36.178B
Market capitalization	84.63B (3/08)**	83.48B (3/07)**

Amgen Inc.

*biotechnology company

	YE 2007	YE 2006
Revenue	$14.771B	$14.268B
Net income	$3.166B	$2.950B
Earnings per share	$2.83/share	$2.51/share
Average shares outstanding	1.117B	1.176B
Total assets	$34.639B	$33.788B
Market capitalization	45.854B (3/08)	70.99B (3/07)

AstraZeneca plc

*pharmaceutical company

Parent company of MedImmune Inc.

	YE 2007	YE 2006
Sales	$29.559B	$26.475B
Profit	$5.627B	$6.063B
Earnings per share	$3.74/share	$3.86/share
Average shares outstanding	1.495B	1.564B
Total assets	$47.957B	$29.932B
Market capitalization	60.48B (3/08)**	

Bayer Group

*health care company

	YE 2007	YE 2006
Net sales	€32.385B	€28.956B
Net income	€4.711B	€1.683B
Earnings per share	€5.84/share	€2.22/share
Market capitalization	64.97B (3/08)**	

Biogen Idec Inc.

*biotechnology company

	YE 2007	YE 2006
Revenue	$3.172B	$2.683B
Net income	$638.172M	$217.511M
Earnings per share	$2.02/share	$0.64/share
Average shares outstanding	315.836M	338.585M
Total assets	$8.629B	$8.553B
Market capitalization	19.059B (3/08)	14.60B (3/07)

Bristol-Myers Squibb Co.

*pharmaceutical company

	YE 2007	YE 2006
Revenue	$19.348B	$17.256B
Net income	$2.165B	$1.585B
Earnings per share	$1.10/share	$0.81/share
Average shares outstanding	1.970B	1.960B
Market capitalization	42.95B (3/08)**	58.85B (4/07)*

Cephalon Inc.

*biopharmaceutical company

	YE 2007	YE 2006
Revenue	$1.773B	$1.764B
Net <loss> income	<$191.704M>	$144.816M
Earnings <loss> per share	<$2.88/share>	$2.39/share
Average shares outstanding	66.597M	60.507M
Total assets	$3.506B	$3.045B
Market capitalization	4.468B (3/08)	4.07B (3/07)

Eli Lilly and Co.

*pharmaceutical company

Parent of ICOS Corp.

	YE 2007	YE 2006
Revenue	$18.634B	$15.691B
Net income	$2.953B	$2.663B
Earnings per share	$2.71/share	$2.45/share
Average shares outstanding	1.090B	1.086B
Market capitalization	58.91B (3/08)**	57.41B (3/07)