



## U.S. and Worldwide Monoclonal Antibody Medicine: Current Status and Future Trends

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### RESEARCH OBJECTIVES

Antibody drugs were a \$24 billion business in 2007. Although most pharmaceuticals are chemically synthesized small molecules, antibodies are large and complex proteins (immunoglobulins) that act as the human body's own weapons against infections, diseases and abnormal cancer cells. *Monoclonal antibodies* (MAbs) mimic the body's immune system with the antibody working as the drug molecule, only MAbs are engineered artificially outside the body, in the laboratory, rather than by a person's own immune system. Furthermore, MAbs are engineered to binding to one particular antigen only. MAbs are thus important tools for medicine as extremely targeted therapies for treating patients with severe diseases – especially autoimmune conditions and cancers.

This report analyzes the activities of the leading biopharmaceutical companies with antibody-based drug products currently on the market or scheduled for introduction soon. The focus is MAb therapeutics used for treating a disease or condition (as opposed to MAbs used as a diagnostic or for research). The report details the status of drug makers' antibody pipelines; their alliances, M&As and investments to develop and commercialize new MAb drugs; and their standing in the battle for market share and bringing a new best-selling drug to patients. Technological progression in the development of antibody and protein-based human therapies is overviewed. This report is part of Fuji-Keizai's ongoing efforts to track the U.S. and global biopharmaceuticals marketplace.

## 1. MARKET OVERVIEW

### Timeline of FDA approval of therapeutic MABs (drugs now on the U.S. market)

	1986-2000	2001	2002	2003	2004	2005	2006	2007	2008 (YTD)	Cumulative
# of New MAb drugs										
Drug brand names										

### Market Players

Four large pharmaceutical companies have cornered the largest part of the current market for monoclonal antibodies: Roche through its Genentech subsidiary; Johnson & Johnson through its Centocor subsidiary; Abbott Laboratories; and AstraZeneca through its MedImmune biologics unit. They are market leaders because they have already commercialized one or more profitable MAb drugs and have others in clinical development. Their currently marketed drugs continue to be studied and authorized for treatment of additional disease indications beyond the initial disease approval. They have strong intellectual property positions for their MAb discoveries, which is due in part to the FDA lacking a process for approving generic (or competitive) versions of their drugs.

The global Big Pharma companies did not build their monoclonal antibody businesses from scratch, but mostly acquired access to their MAb products and capabilities:

- Johnson & Johnson (U.S.): -----
- Roche (Switzerland): -----

Key Players in the Antibody Medicine Market *	Business Model
<p><b>Large Pharmas</b>  <i>Roche/Genentech</i>  <i>J&amp;J/Centocor</i>  <i>AstraZeneca/MedImmune</i>  <i>Abbott Laboratories</i>            GSK, Eli Lilly, Wyeth,            Bristol-Myers Squibb</p>	

<b>Biotechnology Companies</b> <i>Amgen</i> <i>Biogen Idec</i> <i>UCB Pharma</i> <i>Novartis</i> Alexion Pharmaceuticals, Genmab, ImClone, Genzyme, Immunogen, PDL BioPharma	
<b>Technology/Platform Companies</b> Medarex, Dyax Corporation, XOMA, EvoGenix, MorphoSys Technologies, Micromet	
<b>VC-funded Start-ups</b> AVEO Pharma, Epitomics, OncoMed, Raven Biotechnologies	
<b>Contract Biopharma Manufacturers</b> Goodwin BioTechnology (Florida) Lonza (Switzerland) Crucell (Netherlands) DSM Biologics (Netherlands)	

\*Companies in *italics* are covered in Section 6 of this report.

## 2. PRODUCT TRENDS

### 2.1 Current Products

Company Name	Product Name	Introduction	Target Body Therapy Area	2007 Sales Amount (\$M) *see Notes
<b>Immunology</b>				
<b>Oncology</b>				
<b>Immunology &amp; Oncology</b>				
<b>Hematology</b>				
<b>Cardiovascular</b>				
<b>Infectious Disease</b>				
<b>Ophthalmology</b>				

### 2.2 Company Pipelines

The following is a list of 100 MAb's in preclinical to phase 3 trial, based on Fuji-Keizai's survey of the pipeline of the major pharmaceutical players. This partial list represents one-fifth of the 440 MAb's known to be under study as of 1Q08. The list is subject to change because drugs may be withdrawn from trial at any time. One MAb on our list, tremelimumab (Pfizer/Medarex), had a setback when its late-stage trial was suspended in April 2008.

Company Name	Project Name	Current Stage	Target Body Therapy Area	Important Items
		Phase 3	I	

## 3. TECHNOLOGY TRENDS OVERVIEW: CURRENT TO FUTURE

The diversity and complexity of monoclonal antibody drugs are the result of different antibody structures (e.g., different arrangements of genes in the variable regions of the antibody), different targets (the proteins that antibodies interact with by binding to them)

and different mechanisms of action.

### 3.1 Antibody and Immune System Overview

#### 3.1.1 Antibody Structure

#### 3.1.2 Antibody Targets

In addition to differences in MAb structure, there are differences in targets. Monoclonal antibodies are made in the lab as drugs to act against highly specific targets associated with specific disease. The "target" refers to a particular protein in the body that is crucial to the drug activity of a given MAb. These targets are different glycoproteins, glycolipids and carbohydrate molecules that exist on the outside of tumor cells. Antigen-specific receptors needed for immune cell (B-cell or T-cell) activation and proliferation are also targets. Monoclonal antibodies to growth factors or their receptors play an especially important role in cancer therapy. There are dozens of targets under study for MAb cancer drug candidates, but researchers appear to consider some targets to be more important than others.

#### Important targets for anti-cancer MAbs

Target	Drug or Drug Candidate	Status

#### 3.1.3 Mechanisms of Action

Monoclonal antibodies interact in unique ways with other proteins they bind to. There are three basic mechanisms of action that define how MAb therapeutic drugs work:

#### Variety of MAbs: different technologies, structures, targets, action mechanisms

Brand Name	Technology	Structure	Target	Mechanism of Action

### 3.2 Antibody Generation: Current and Emerging Technologies

Monoclonal antibodies are made from one type of immune cell (the antibody parent cell); as such, they are all clones of a single parent cell and can produced in the laboratory in

commercial quantities using biotechnology techniques. Various approaches to MAb development have evolved, including hybridomas, immunoconjugates, antibody fragments

### Evolution of MAb technology

#### 3.2.1 Hybridoma Technology

Platform players:

#### 3.2.2 Genetically Engineered and Humanized MABs

##### Transgenic Animal Technologies

Platform players:

##### Library Technologies (phage display)

Platform players:

##### Optimization and Protein Engineering

Platform players:

## 4. MARKET ANALYSIS

### 4.1 Monoclonal Antibody Market Forecast (Total) 2006-2012

Makers of Marketed MAb drugs (* see Findings)	MAb Product Revenues (\$ Million)							Growth (%)
	2006	2007	2008e	2009e	2010e	2011e	2012e	
Abbott								
<b>SUBTOTAL</b>								
Possible new MABs approved 2009 & later								
<b>TOTAL</b>								

### Key Findings

**Late-stage MAb drugs: anticipated timeline for approval: 2009-2011**

Drug Name & Maker	Therapy Area	2009	2010	2011

**Growth Drivers**

**Market Impediments/Challenges**

**4.2 Breakdown by Company**

<p><b>Pie Chart</b></p>
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**Key Findings**

**4.3 Breakdown by Therapy Segment**

Therapy Segment	MAb Product Revenues (\$ Million)								Includes sales of:	Growth (%)
	2006	2007	2008e	2009e	2010e	2011e	2012e			
Oncology										
Immunology (sub-segments)										
Autoimmune/inflammatory										
Organ Transplants										
Hematology (anemia)										
Neurology (MS)										
Respiratory										
Cardiovascular										
Ophthalmology										
TOTAL										

**Two Pie Charts: 2008 vs. 2012**

**Monoclonal antibody share of total immunology drug market (by revenues): 2008 -2012**

### **Therapy Market Growth Drivers: Immunology and Cancer**

**Two Pie Charts: 2008 vs. 2012**

**Monoclonal antibody share of total cancer drug market (by revenues): 2012**

**Pie Chart**

**Therapy areas, by market share ( %): 2007 revenues of all MABs**

### **4.4 Breakdown by Therapies in the Pipeline (2012 Market Potential)**

**Pie Chart**

**Percentage of MAb drugs in pipeline, by therapy area (post-2008 potential)**

Source: Fuji-Keizai USA, based on survey of 100 pipeline drugs

**Bar Graph**

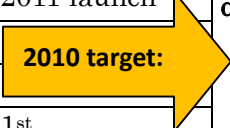
**MAB drug candidates in development, by specific disease indication**

**Pie Chart**


**Growth Driver: Alzheimer's MAb pipeline**

**Findings**

**Infectious disease MAb pipeline**

Maker	Drug Name	Stage	Therapy Market	Comment	
				2009 launch	<b>\$93B infectious disease market</b> – MAbs will compete mostly with new vaccines in drug pipelines
				2011 launch	
				<b>2010 target:</b> 	
				1 <sup>st</sup> polyclonal Ab drug in clinical trial	

**Osteoporosis MAb pipeline**

Maker	Drug	Stage	Therapy Market	Comment	
				2008/09 launch – revenue projection of \$100M in first year	<b>\$10-\$12B market for osteoporosis drugs</b> 
				<b>2010 target:</b>	

## 4.5 Breakdown by Products

### Top 5 monoclonal antibody drugs, by sales

Drug	Maker *see Note	Product Revenues (\$ Million)							
		2006	2007	2008	2009	2010	2011	2012	Growth %
<b>Total</b>									

### Market share (%) of top 5 MAb drugs, 2007

### Growth Drivers of the Top 5

#### Multiple Indications as Growth Driver for Best-selling MABs

Drug makers have ongoing, post-marketing trials to explore additional therapy markets for their existing, already-successful products. Rituxan's mechanism of action is being explored for multiple sclerosis. Regulatory approval is

#### Revenue for dual-purpose cancer drug Avastin

Revenue (\$B)	2008	2009	2010	2011	2012
Colorectal cancer (original indication since 2004)					
Breast cancer (approved March 2008)					

#### Premium Pricing as Growth Driver and Inhibitor

Drug	Unit Price*	Monthly or Yearly Cost
	\$600/syringe	\$13,000-\$18,000/year  Abbott Humira assistance program will cover up to \$325/month of the patient's co-payment

\*Prices estimated by various insurance sources.

#### Finding

- High prices for monoclonal antibody therapies are another factor that have fueled yearly sales growth and allowed drug makers to turn monoclonal antibodies into

### MAb oncology products, by sales

Drug	Maker	Product Revenues (\$Million)							
		2006	2007	2008	2009	2010	2011	2012	Growth %
<b>Subtotal</b>									
Rituxan est. oncology rev.									
<b>Tota</b>									

Source: Fuji-keizai USA

### Growth Drivers for Cancer MAb Products

- Herceptin and Avastin and Rituxan are the leading cancer immunotherapy drugs and are discussed in the previous section on the top-5 drugs.
- The most important of the other cancer MABs is Eribitux. It was launched

### Immunology MAb products, by sales

Drug	Maker	Product Revenues (\$Million)							
		2006	2007	2008	2009	2010	2011	2012	Growth %
<b>Subtotal</b>									
Rituxan est. immunology rev.									
<b>Tota</b>									

Source: Fuji-keizai USA

### Growth Drivers for Autoimmune Disease MAb Products

The market leaders are Remicade and Humira, which are discussed in the previous section on the

### Other MAB commercialized products, by sales

Drug	Maker *see Note	Product Revenues (\$ Million)							
		2006	2007	2008	2009	2010	2011	2012	Growth %
ReoPro									

TOTAL									
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### Growth Drivers and Impediments in Other Disease Markets

- In other disease markets, there is only one commercially approved monoclonal antibody drug commercially available at

### 4.6 Breakdown by Technology

<b>Pie Chart</b>	
Source: Fuji-Keizai USA	
<b>Technology</b>	<b># Commercialized MABs</b>
Chimeric	
Chimeric fragment	
Fully Human	
Humanized	
Humanized fragment	
Humanized conjugate	
Murine	
Murine conjugate	2

<b>Pie Chart</b>
Source: Fuji-Keizai survey of sampling of 100 pipeline products

<b>Technology</b>	<b># Pipeline Drug Candidates (sample size=95)</b>
Conjugated antibody drugs	
Conjugated antibody fragments	
Fully Human	
Multifunctional Abs	
Peptibody (peptide/Ab hybrid)	
Full-sized, naked, humanized or chimeric	

## 5. M&A, ALLIANCE MAP

### 5.1 MAb and related biologics M&A activity: 2005-2008 (YTD)

Year	Buyer	Company Acquired	Asset Acquired	\$ Value
<b>Large Acquisitions</b>				
2008				\$3.4 B
<b>Mid-Size and Small Acquisitions</b>				
2008			Technology to link therapeutic peptides to an antibody scaffold	

Source: Individual company press releases and news archives

### Key Findings

Mergers & acquisitions are a continuing trend in the pharmaceuticals industry. The growing importance of large-molecule drugs is one of the main drivers of these deals.

### Top 12 Pharmaceuticals (by 2007 sales) and MAb acquisitions or alliances

Company	2007 revenues (\$ M)	MAb Acquisitions: 1999-2008 (YTD)	MAb Acquisition Value
Pfizer			

Source: Fuji-keizai USA

## 6. COMPANY ANALYSIS (8 key players)

### 6.1 ABBOTT LABORATORIES

#### Profile of Monoclonal Antibody Business

##### Abbott's currently marketed MAb drugs

Drug Name	Target Therapy Area	Comment
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## Market Superiority

## M&A Strategy

## Company Pipeline Analysis

### Technology pipeline analysis

- **Proprietary DVD-Ig technology** – In October 2007, Abbott announced it had developed
- **Third-party technology** – Abbott is using quantitative proteomics technologies and the CellCarta platform (from Caprion Proteomics) to study human lung cancer tissues and

### Abbott MAb and protein-based drugs in development

Drug Name	Stage	Target and/or Therapy	Comment
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### Target pipeline analysis

## 7. VENTURE COMPANY ACTIVITY

We chose 20 privately held companies to profile using one or more of three indicators: 1) funding or deals with key industry partners and investors; 2) the company's technology for MAb drug development or production and its potential for commercialization; and 3) drug sales targets from the company (if available).

## 8. Key Findings