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Marketed therapeutic antibodies compendium

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Therapeutic monoclonal antibodies (mAbs) are currently being approved for marketing in Europe and the United States, as well as other countries, on a regular basis. As more mAbs become available to physicians and patients, keeping track of the number, types, production cell lines, antigenic targets and dates and locations of approvals has become challenging. Data are presented here for 34 mAbs that were approved in either Europe or the United States (US) as of March 2012, and nimotuzumab, which is marketed outside Europe and the US. Of the 34 mAbs, 28 (abciximab, rituximab, basiliximab, palivizumab, infliximab, trastuzumab, alemtuzumab, adalimumab, tositumomab-I131, cetuximab, ibrituximab tiuxetan, omalizumab, bevacizumab, natalizumab, ranibizumab, panitumumab, eculizumab, certolizumab pegol, golimumab, canakinumab, catumaxomab, ustekinumab, tocilizumab, ofatumumab, denosumab, belimumab, ipilimumab, brentuximab) are currently marketed in Europe or the US. Data for six therapeutic mAbs (muromonab-CD3, nebacumab, edrecolomab, daclizumab, gemtuzumab ozogamicin, efalizumab) that were approved but have been withdrawn or discontinued from marketing in Europe or the US are also included.

Of the 28 mAbs currently marketed in the European Union or the US, 26 are marketed in Europe and 27 are marketed in the US, with 25 marketed in both regions (**Table 1**). Catumaxomab is approved in Europe but not the US; tositumomab-I131 is marketed in the US but not Europe. Brentuximab vedotin was approved in the US in 2011 and, as of March 2012, a marketing application for the mAb is undergoing review by the European Medicines Agency.[1] Of the 28 mAbs that are marketed in one or the other region, 43% (12/28) are produced in Chinese hamster ovary (CHO) cells, 25% (7/28) are produced in SP2/0 cells,[2] 18% (5/28) are produced in NS0 cells,[3] and 7% (2/28) are produced in hybridomas. The remaining two products (ranibizumab, certolizumab pegol) are antigen-binding fragments (Fab) that are produced in *E. coli*. Humanized and human mAbs comprise 36% (10/28) and 32% (9/28) of the total, respectively, while 21% (6/28) are chimeric and 11% (3/28) are murine. Most (75%; 21/28) are canonical full-length mAbs. Of the 7 non-canonical mAbs, three (abciximab, ranibizumab, certolizumab pegol) are Fab, with one of these (certolizumab pegol) pegylated; two (tositumomab-I131, ibrituximab tiuxetan) are radiolabeled when administered to patients; one (brentuximab vedotin) is an antibody-drug conjugate (ADC); and one is bispecific (catumaxomab). Although 16 marketed mAbs target unique antigens, CD20 and tumor necrosis factor are each targeted by 4 mAbs, and epidermal growth factor receptor (EGFR) and vascular endothelial growth factor are each targeted by 2 mAbs. If approved, pertuzumab, which is undergoing regulatory review in Europe and the US as a treatment for breast cancer, would be one of 2 mAbs that target human epidermal growth factor receptor 2 on the market.

In addition to the 28 mAbs currently marketed, six mAbs were approved in at least one country of Europe or in the US, but were subsequently withdrawn or discontinued from marketing for various reasons (**Table 2**). First approved in the US in 1986, muromonab-CD3 (Orthoclone OKT3®) was a murine IgG2a used to treat acute kidney allograft rejection; however, manufacturing was discontinued in 2010 due to the availability of other treatments with similar efficacy and fewer side effects, and declining sales.[4,5] Nebacumab (Centoxin®), a human IgM, was approved in The Netherlands, Britain, Germany and France during 1991 as a treatment for Gram-negative sepsis,[6] but the product was subsequently withdrawn for safety, efficacy and commercial reasons.[7] The murine anti-epithelial cell adhesion molecule (EpCAM) edrecolomab (Panorex®) was approved in Germany in 1995 as an adjuvant treatment for colon cancer, but subsequently withdrawn because of the product's lack of efficacy.[8] Daclizumab was first approved in 1997 for prophylaxis of acute organ rejection in patients receiving renal transplants, but the product was voluntarily withdrawn from the market in Europe effective January 1, 2009 [9] and discontinued for the US market because of the availability of alternative therapy and the diminished market demand.[10] The first ADC to be approved, gemtuzumab ozogamicin was marketed in the US for a decade before being voluntarily withdrawn in 2010. The product was approved under the accelerated approval mechanism as a treatment for acute myeloid leukemia (AML), but was withdrawn when a confirmatory clinical trial and post-approval use did not show evidence of clinical benefit in AML patients.[11] Efalizumab (Raptiva®) was approved in the US and Europe in 2003 and 2004, respectively, as a treatment for adults with moderate to severe plaque psoriasis, but the product was

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Table 1. Therapeutic monoclonal antibodies marketed or in review in the European Union or United States

International non-proprietary name (Trade name)	Manufacturing cell line	Type	Target	First EU (US) approval year
Abciximab (Reopro®)	Sp2/0	Chimeric IgG1κ Fab	GPIIb/IIIa	1995* (1994)
Rituximab (MabThera®, Rituxan®)	CHO	Chimeric IgG1κ	CD20	1998 (1997)
Basiliximab (Simulect®)	Sp2/0	Chimeric IgG1κ	IL2R	1998 (1998)
Palivizumab (Synagis®)	NS0	Humanized IgG1κ	RSV	1999 (1998)
Infliximab (Remicade®)	Sp2/0	Chimeric IgG1κ	TNF	1999 (1998)
Trastuzumab (Herceptin®)	CHO	Humanized IgG1κ	HER2	2000 (1998)
Alemtuzumab (MabCampath, Campath-1H®)	CHO	Humanized IgG1κ	CD52	2001 (2001)
Adalimumab (Humira®)	CHO	Human IgG1κ	TNF	2003 (2002)
Tositumomab-I131 (Bexxar®)	Hybridoma	Murine IgG2aλ	CD20	NA (2003)
Cetuximab (Erbitux®)	Sp2/0	Chimeric IgG1κ	EGFR	2004 (2004)
Ibritumomab tiuxetan (Zevalin®)	CHO	Murine IgG1κ	CD20	2004 (2002)
Omalizumab (Xolair®)	CHO	Humanized IgG1κ	IgE	2005 (2003)
Bevacizumab (Avastin®)	CHO	Humanized IgG1κ	VEGF	2005 (2004)
Natalizumab (Tysabri®)	NS0	Humanized IgG4κ	α4-integrin	2006 (2004)
Ranibizumab (Lucentis®)	*E. coli*	Humanized IgG1κ Fab	VEGF	2007 (2006)
Panitumumab (Vectibix®)	CHO	Human IgG2κ	EGFR	2007 (2006)
Eculizumab (Soliris®)	NS0	Humanized IgG2/4κ	C5	2007 (2007)
Certolizumab pegol (Cimzia®)	*E. coli*	Humanized IgG1κ Fab, pegylated	TNF	2009 (2008)
Golimumab (Simponi®)	Sp2/0	Human IgG1κ	TNF	2009 (2009)
Canakinumab (Ilaris®)	Sp2/0	Human IgG1κ	IL1b	2009 (2009)
Catumaxomab (Removab®)	Hybrid hybridoma	Rat IgG2b/mouse IgG2a bispecific	EpCAM/CD3	2009 (NA)
Ustekinumab (Stelara®)	Sp2/0	Human IgG1κ	IL12/23	2009 (2009)
Tocilizumab (RoActemra, Actemra®)	CHO	Humanized IgG1κ	IL6R	2009 (2010)
Ofatumumab (Arzerra®)	NS0	Human IgG1κ	CD20	2010 (2009)
Denosumab (Prolia®)	CHO	Human IgG2κ	RANK-L	2010 (2010)
Belimumab (Benlysta®)	NS0	Human IgG1λ	BLyS	2011 (2011)
Raxibacumab (Pending)	NS0**	Human IgG1κ	*B. anthrasis* PA	NA (In review)
Ipilimumab (Yervoy®)	CHO	Human IgG1κ	CTLA-4	2011 (2011)
Brentuximab vedotin (Adcentris®)	CHO	Chimeric IgG1κ; conjugated to monomethyl auristatin E	CD30	In review (2011)
Pertuzumab (Pending)	CHO	Humanized IgG1κ	HER2	In review (in review)

Note: Information current as of March 10, 2012. *Country-specific approval; approved under concertation procedure **Product manufactured for Phase 1 study in humans. Abbreviations: BLyS, B lymphocyte stimulator; C5, complement 5; CD, cluster of differentiation; CHO, Chinese hamster ovary; CTLA-4, cytotoxic T lymphocyte antigen 4; EGFR, epidermal growth factor receptor; EpCAM, epithelial cell adhesion molecule; Fab, antigen-binding fragment; GP glycoprotein; IL, interleukin; NA, not approved; PA, protective antigen; RANK-L, receptor activator of NFκb ligand; RSV, respiratory syncytial virus; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor. Sources: European Medicines Agency public assessment reports, United States Food and Drug Administration (drugs@fda), the international ImMunoGeneTics information system® (www.imgt.org/mAb-DB/index).

voluntarily withdrawn from both markets in 2009 because of the risk of side effects, including progressive multifocal leukoencephalopathy.[12,13]

The European Union and the US are not necessarily the first or only markets for therapeutic mAbs (**Table 3**). Nimotuzumab, a humanized mAb that targets EGFR, was developed at the Center of Molecular Immunology in Cuba. The mAb is marketed in over 20 countries, including Brazil, India and China, as a treatment for head and neck cancer or glioma, but it is not approved in the EU, US or Japan.[14] Mogamulizumab is a defucosylated humanized anti-CC chemokine receptor 4 (CCR4) antibody developed by Kyowa Hakko Kirin Co., Ltd.[15] The mAb is approved in Japan as a treatment for adult T-cell leukemia-lymphoma and peripheral T-cell lymphoma.

The 35 marketed mAbs, most of which are canonical full-length IgG1, paved the way for the next generation of antibody-based therapeutics such as ADCs, bispecific antibodies, engineered antibodies and antibody fragments or domains. The commercial pipeline includes ~350 mAbs now being evaluated in clinical studies

Table 2. Therapeutic monoclonal antibodies withdrawn or discontinued from marketing in the European Union or United States

International proprietary name (Trade name)	Manufacturing cell line	Type	Target	First EU (US) approval year
Muromonab-CD3 (Orthoclone OKT3®)	Hybridoma	Murine IgG2a	CD3	1986* (1986)
Nebacumab (Centoxin®)	Hybridoma	Human IgM	Endotoxin	1991* (NA)
Edrecolomab (Panorex®)	Hybridoma	Murine IgG2a	EpCAM	1995* (NA)
Daclizumab (Zenapax®)	NS0	Humanized IgG1κ	IL2R	1999 (1997)
Gemtuzumab ozogamicin (Mylotarg®)	NS0	Humanized IgG4κ	CD33	NA (2000)
Efalizumab (Raptiva®)	CHO	Humanized IgG1κ	CD11a	2004 (2003)

Note: Information current as of March 10, 2012. *European country-specific approval. Abbreviations: CD, cluster of differentiation; CHO, Chinese hamster ovary; EpCAM, epithelial cell adhesion molecule; IL, interleukin; NA, not approved. Sources: European Medicines Agency public assessment reports, United States Food and Drug Administration (drugs@fda), the international ImMunoGeneTics information system® (www.imgt.org/mAb-DB/index).

Table 3. Therapeutic monoclonal antibodies approved outside the European Union or United States

International proprietary name (Trade name)	Manufacturing cell line	Type	Target	First approval year
Nimotuzumab (TheraCIM®, BIOMAB-EGFR®)	NS0	Humanized IgG1κ	EGFR	1999
Mogamulizumab	[Not found]	Humanized IgG1κ	CCR4	2012

Note: Information current as of March 30, 2012. Abbreviations: CCR, chemokine receptor; EGFR, epidermal growth factor receptor.

around the world as treatments for many indications, including cancer, immunological disorders and infectious diseases.[16] The compendium of marketed therapeutic antibodies may thus be substantially larger in the future.

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