

## 258 RSV Mab, rDNA

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**Palivizumab - Synagis; MEDI-493; respiratory syncytial virus (RSV) monoclonal antibody, recombinant**

Company roles:

- [Abbott Laboratories, Inc.](#) -- World mark.
- [Alusuisse-Lonza Group](#) -- Parent
- [AstraZeneca plc](#) -- Parent
- [Boehringer Ingelheim Pharma KG](#) -- Manuf.
- [Celltech Biologics plc](#) -- Former
- [Celltech Group plc](#) -- Tech.
- [Chiron Corp.](#) -- Manuf. other
- [DRI Capital](#) -- Tech.
- [Genentech, Inc.](#) -- Tech. ; Patent dispute
- [Johnson & Johnson Co. \(J&J\)](#) -- Patent dispute
- [Lonza Biologics plc](#) -- Tech.
- [MedImmune, Inc.](#) -- Manuf. ; R&D ; Tech. ; USA mark.
- [Novartis AG](#) -- Parent
- [PDL Biopharma, Inc. \(PDL\)](#) -- Tech.
- [UCB Group S.A.](#) -- Parent
- [University of Glasgow](#) -- Tech.
- [Cambridge Antibody Technologies, Inc.](#) -- Tech.

Full monograph

### 258 RSV Mab, rDNA

**Palivizumab - Synagis; respiratory syncytial virus (RSV) monoclonal antibody, recombinant**

**Status - approved; marketed**

**Organizations involved:**

MedImmune, Inc. - Manuf.; R&D; Tech.; USA mark.

AstraZeneca plc - Parent

Abbott Laboratories - World mark.

Boehringer Ingelheim Pharma KG - Manuf.

Chiron Corp. -- Manuf. other

Novartis AG - Parent

Protein Design Labs, Inc. - Tech.

Celltech Group plc - Tech.; Patent dispute

Genentech, Inc. - Tech.; Patent dispute

UCB Bioproducts S.A. - Parent

Lonza Biologics plc - Tech.

Alusuisse-Lonza Group - Parent

University of Glasgow - Tech.

DRI Capital. - Tech.

Cambridge Antibody Technologies, Inc. - Tech.

Johnson & Johnson (J&J) - Patent dispute

**Cross Ref.:** See the Monoclonal Antibodies entry (#300). See also the entry below for motavizumab, a next-generation version of this product; and the RSV Immune Globulin (RespiGam) entry in the human blood products section, which had been replaced by this product.

**Description:** Synagis is a lyophilized (freeze-dried) formulation of a recombinant humanized (chimeric murine-human) IgG1kappa monoclonal antibody glycoprotein (palivizumab) with specificity for an epitope in the A antigenic site of the F (fusion) protein of respiratory syncytial virus (RSV). Palivizu-mab is expressed from a stable murine (mouse) myeloma cell line (NS0). Palivizumab was derived from a murine monoclonal antibody and humanized by grafting of the complementarity determining regions (CDR) of the murine monoclonal antibody Mab 1129 into a human antibody framework with an IgG1 constant region. Synagis was the first monoclonal antibody product approved in the U.S. for an infectious disease indication. At the time, its initial launch was the most successful of any biopharmaceutical product, in terms of rapid gain of sales and market share. Palivizumab is composed of two heavy chains (50.6 kDa each) and two light chains (27.6 kDa each), contains 1-2% carbohydrate by weight and has a molecular weight of 147.7 kDa  $\pm$  1 kDa (MALDI-TOF). A new liquid formulation of Synagis was approved in July 2004, and is expected to be launched in time for the 2005/2006 RSV season.

Palivizumab is essentially a murine monoclonal antibody which has been "humanized" by replacement of comparable human for murine gene/protein sequences, while retaining the antibody-antigen affinity and active portions of Mab 1129, a murine RSV F protein-specific monoclonal antibody. See also the History and Patents sections for

further information. The palivizumab molecule, originally designated MEDI-493, is a composite of murine (5%) and human (95%) antibody sequences. The configuration of the murine complementarity determining regions (CDRs; antigen-binding portion) into the human immunoglobulin (IgG1) framework shields the molecule from inducing significant human anti-mouse antibody (HAMA; immune rejection of murine IgG) reactions in clinical use. Simply stated, the active RSV-neutralizing portions (CDRs) of the source mouse (murine) monoclonal antibody (Mab 1129) are spliced into a human antibody (immunoglobulin) constant framework. The human heavy chain sequence was derived from the constant domains of human immunoglobulin G1 (IgG1) and the vari-able framework regions of the VH genes Cor and Cess. The murine sequences were derived from murine Mab 1129 through a process which involved the grafting of the murine complementarity determining regions (CDRs) into the human antibody frameworks. The human light chain sequence was derived from the constant domain of the C-kappa and the variable framework regions of the VL gene K104 with J-kappa-4.

Humanization of the murine monoclonal antibody avoids human anti-mouse antibody (HAMA) reactions or recognition of the antibody as foreign, i.e., palivizumab presents itself as a human antibody. Humanized antibodies, such as Synagis, can have a longer in vivo half-life and be less immunogenic than conventional murine monoclonal antibodies. An article describing the development of Synagis was published in the Journal of Infectious Diseases (vol. 176, no. 5, p. 1215-24, November 1997).

Palivizumab specifically binds the F or fusion surface protein of respiratory syncytial virus (RSV). The F protein is required for fusion of RSV-infected cells with other infected cells, forming complexes of fused RSV-infected cells termed syncytia (syncytium is singular form). Syncytia are composed of masses of protoplasm with no cell membranes separating cell nuclei. The F protein, when expressed on the surface of RSV-infected cells, allows fusion with other the F proteins of other RSV-infected cells.

Synagis is supplied in a single use vial containing 100 mg of sterile lyophilized palivizumab for intramuscular injection after reconstitution with Sterile Water for Injection. After reconstitution, Synagis contains the following excipients: 47 mM histidine, 3.0 mM glycine and 5.6% mannitol. Synagis contains no preservatives. Synagis has a pH of 6 (range 5.0-7.0) and osmolality of 462 mmol/kg. The product should be stored at 2-8°C (refrigerated) and has a half-life of two years.

A new liquid formulation of Synagis, approved in July 2004, slated to replace the current lyophilized powder version, will be launched in fall 2004. This will be packaged in 50 mg and 100 single-use vials, with no preservatives

Each 100 mg vial contains 120 mg palivizumab (100 mg/mL), 4.7 mg histidine, and 0.1 mg glycine in 1.2 mL Water for Injection, for withdrawal and intramuscular injection of 100 mg palivizumab in 1 mL. Each 50 mg vial contains approximately 70 mg palivizumab (100 mg/mL), 2.6 mg histidine, and 0.08 mg glycine in 0.7 mL Water for Injection, for withdrawal and injection of 50 mg in 50 mL. There is an overfill in the vials to allow for

withdrawal of the specified dose.

**Nomenclature:** RSV Mab1, rDNA [BIO]; Synagis [TR]; Palivizumab [FDA USAN INN]; respiratory syncytial virus (RSV) mono-clonal antibody [SY]; MEDI-493 [SY]; 60574-4111-01 [NDC]

Note, "Synagis" may best be used to refer to the product and "palivizumab" may best be used to refer to the active monoclonal antibody ingredient. However, both of these terms and synonyms are often used to refer to the product/formulation and/or active ingredient.

**Biological:** RSV was originally isolated from chimpanzees in 1956. RSV is a pleomorphic virus, a member of the family of Paramyxoviridae, comprising a single strand, sense-negative RNA genome, which is tightly associated with viral protein to form the nucleocapsid. RSV is comprised of two major groups (A and B). The RSV genome codes for three transmembrane surface proteins (F, G, and SH), 2 matrix proteins (M and M2), 3 nucleocapsid proteins (N; P and L) as well as for 2 non-structural (NS1 and NS2) protein. The surface fusion (F) and attachment (G) proteins are the only viral components capable of inducing RSV-neutralizing antibodies.

Although first isolated in 1956, to date, efforts to produce an effective antigen-based prophylactic RSV vaccine have been unsuccessful. A major obstacle to development of such a vaccine has been safety. A formalin-inactivated RSV vaccine developed in the 1960s resulted in high seroconversion rates but caused an increased incidence of RSV lower respiratory tract disease and death in immunized children upon exposure to wild virus (Kapikian, A.Z., et al., Am. J. Epidemiol. 89:405, 1969) compared to patients receiving placebo.

The F protein, a 70 kDa disulfide linked heterodimer, mediates fusion of the viral envelope with the plasma membrane and syncytium formation; has a high degree of genetic and antigenic homology between RSV group A and RSV group B; and has been antigenically stable over years. Antibodies against the F protein neutralize both RSV group A and B isolates.

Palivizumab specifically binds with high affinity ( $K_d = 0.96 \text{ nM}$ ) to the F protein of RSV, neutralizing RSV and also inhibiting spread by syncytia formation. Palivizumab is 50 to 100 times more potent than RSV immune globulin (RespiGam from MedImmune; see related entry #781) in a cotton rat model of RSV infection, with serum concentrations of  $>$  or  $= 40 \mu\text{g/ml}$  reducing RSV replication (viral load) about 100-fold greater. Neutralization activity in vitro has been demonstrated against 57 RSV isolates of both A and B strains.

Palivizumab has a pharmacokinetic profile in adults similar to that of human immune globulin (IgG1) with a mean half-life of 18 days and a half-life of 20 days in infants (<2 years old). As reported in the Journal of Infectious Diseases, December 1998, Synagis was shown to significantly reduce RSV titers in the tracheal secretions of severe RSV-infected intubated infants compared to placebo.

Synagis is the result of about eight years of intensive development by MedImmune. Studies by Beeler and others in the mid-late 1980s established that RSV strains (serotypes A and B) share a common antigenic surface glycoprotein, particularly epitopes of the A antigenic site of the F (fusion) glycoprotein. Antibodies to this site were shown to neutralize RSV and/or inhibit RSV fusion (syncytia formation) activity. MedImmune then set out to identify and refine an IgG monoclonal antibody to this target (to take the place of RespiGam) First, mice were infected with human RSV strain A2 and their spleens were harvested to obtain B-cells primed to make RSV IgG antibody. Hybridoma cell lines for expression of monoclonal antibodies were developed by standard methods (Kohler, et al.; fusion with myeloma cells). Resulting monoclonal antibodies (Mab) were screened for antigen specificity. One murine monoclonal antibody (hybridoma), MAb 1129, was selected for its optimal specificity for an epitope of the A site in the RSV F glycoprotein.

Using technology nonexclusively licensed from Protein Design Labs. (see Tech. transfer section), murine MAb 1129 was humanized. The MAb 1129 binding site, in the variable regions of the Fab fragment of the antibody, was sequenced to determine its Complimentary Determining Regions (CDRs). Six CDRs were found to be essential and by recombinant methods these were grafted to the variable framework of a human IgG1 antibody relying on the architecture of V domains (i.e., chimeric engineering of the variable regions). IgG1 was selected as the Fc fragment (constant human region) for the recombinant antibody because it has the optimal effector properties (pharmacokinetics, complement and cell-mediated killing) among all the IgG isotypes for this therapeutic use. DNA sequences for six desired CDRs were obtained from the murine B-cell that originally produced the MAb 1129 hybridoma, then spliced to DNA that encode for the variable (Fab) and constant (Fc) regions of a normal human IgG1 molecule. This involved use of human VH genes described by Cor and Cess for the heavy chain amino acid sequences, and VL genes K104 with Jk-4 for the light chain amino acid sequences (all of which comprise the entire IgG1 molecule.)

The chimeric gene containing the assembled DNA segments was synthesized via polymerase chain reaction (PCR), and the resultant gene was propagated as a plasmid in Escherichia coli (E. coli). The plasmid propagated in E. coli was isolated, mixed with murine myeloma NS0 cells (which are very efficient in expressing IgG antibody), and exposed to electro-poration (high voltage electricity), allowing the DNA plasmid to enter the nucleus of the myeloma cell and become part of its chromosomal structure (transformation). Glutamine synthetase (GS) selection technology (licensed from Lonza; see Tech. transfer section) and amplification using methionine sulfoxine were used to select an optimally transformed murine NS0 cell line (hybridoma), which is capable of producing about 1 gram of monoclonal antibody/liter of culture. This cell line was expanded and preserved frozen in liquid nitrogen as the Working Cell Bank (WCB). Each myeloma cell derived from the WCB can produce significant quantities of palivizumab.

**Companies:** Synagis was developed by MedImmune, Inc., CBER/FDA est. no. 1252. Development was completed with only 3.5 years from time of submission of the first IND to FDA approval. As discussed below, Synagis is manufactured at facilities in the

U.S. and Germany. MedImmune was acquired by AstraZeneca plc in April 2007.

MedImmune and the Ross Products Div., Abbott Labs., co-promote Synagis in the U.S., and Abbott holds exclusive marketing rights outside of the U.S. MedImmune's sales force concentrates on the 500 largest hospitals in the U.S. with neonatal intensive care units, while the Ross/Abbott sales force concentrates on the 2,000 hospitals with facilities for delivering babies and the 27,000 office-based pediatricians in the U.S. MedImmune is credited with all U.S. sales of Synagis by Ross/Abbott, which receives a 32% commission on sales over an unspecified amount (an amount which MedImmune projected its own 60-person sales force could sell).

The original approval was for product manufactured by MedImmune, CBER/FDA est. no. 1252, at its Gaithersburg, MD, facility (not geared for large-scale manufacture). This was followed by supplemental approval of large-scale manufacture under contract to MedImmune by Boehringer Ingelheim Pharma KG (BI; Biberach/Riss, Germany), CBER/FDA est. no. 1251. BI also fills and packages Synagis produced at its facility. MedImmune paid Boehringer Ingelheim \$14.3 million in 2001, \$26.4 million in 2000, and \$21.1 million in 1999 for production and scale-up of production. MedImmune has firm commitments with BI for production through March 2004 for approximately 43.7 million Euros.

In late 1999, MedImmune received supplemental approval allowing Synagis manufacture at the company's new large-scale facility in Frederick, MD. Product manufactured at this facility supplements that manufactured by Boehringer Ingelheim (BI). Manufacture by MedImmune in Gaithersburg has ceased. MedImmune announced in July 2000 an increase in fermentation batch size from 10,000 to 12,500 liters. BI facilities are reported to have a maximum batch size of 45,000 vials of the 100 mg size and 93,000 of the 50 mg size vials. Even with enhanced yield improvements adopted in 2001, MedImmune will continue to rely upon BI for a portion of worldwide Synagis production for at least the next few years.

In April 1998, MedImmune contracted with Chiron Corp. for filling and packaging of Synagis produced at its Gaithersburg pilot plant and Frederick manufacturing plant. In 2001, this contract was extended for an additional three years.

Drug Royalty Corp. Inc., now DRI Capital, has purchased from undisclosed sources (apparently 2 different sources) for \$9.25 million and later for \$4.97 million undisclosed shares of future Synagis royalties

In Feb. 2005, MedImmune amended its agreement with Abbott, granting Abbott rights for international (ex-U.S.) marketing of motavizumab (see entry below), its next generation RSV Mab currently in Phase III trials. MedImmune has the option to co-promote the product with Abbott in up to seven countries outside of the U.S.

In Aug. 2005, MedImmune amended its U.S. co-promotion agreement with Abbott. Abbott will continue to co-promote Synagis through June 30, 2006, at which time MedImmune will take full responsibility for all U.S. sales. MedImmune expanded its 300- person pediatric sales organization by ~125 in advance of the 2006/2007 RSV

season to replace Abbott's co-promotion efforts. MedImmune will continue to pay a portion of U.S. sales of Synagis to Abbott through 2006. MedImmune will also make additional payments to Abbott, including incentive payments based on the achievement of certain U.S. sales levels of Synagis during the 2005-2006 RSV season. If MEDI-524/Numax (a replacement for Synagis, see below) is not approved for marketing in the U.S. by Sept. 1, 2008, MedImmune will make additional payments to Abbott based upon sales of Synagis for up to two years. This agreement will enable MedImmune to launch and market MEDI-524 without competition with Abbott marketing Synagis. And if this next generation product reaches the market, MedImmune will still have full control of U.S. Synagis sales. Abbott retained its ex-U.S. rights to distribute and market Synagis and motavizumab.

In Sept. 2006, MedImmune broke ground for expansion of its existing Synagis manufacturing facility in Frederick, MD. This \$250-million expansion is the first phase of a multi-phase construction project, and includes construction of facilities for manufacture of other products. Phase 1 of the expansion is expected to be complete in late 2009.

**Manufacture:** MedImmune uses a stirred-tank, fed-batch system for recombinant antibody manufacture. A stable cell line for large-scale production was developed from a murine myeloma cell line (NS0). Twenty-one candidate production cell lines were evaluated for growth rate and secretion of palivizumab. Selection of one cell line, suitable for large-scale production, was based on expression level, growth rate, and stability. The selected transformed cell line can produce about 1 gram palivizumab/liter of culture. The best candidate after cloning resulted in the generation of the Accession Cell Bank (ACB). Cells from one ACB vial were used to establish the Master Cell Bank (MCB). Each MCB vial can be used to prepare a Working Cell Bank (WCB). The MCB was characterized for identity, quality and safety measuring the following parameters: mouse antibody production, isoenzyme analysis, in vivo assay for adventitious viruses, in vitro assay for adventitious viruses, sterility, mycoplasma, extended S+L focus assay, extended XC plaque assay, DNA profiling, cDNA sequences of heavy & light IgG chains, and copy number. The WCB was characterized for sterility, DNA-fingerprinting, mycoplasma, and in vitro assay for adventitious viruses. No evidence of microbial contamination was found. The DNA profile was characterized and the profile was found to be similar to that of the MCB.

Media components are organic chemicals (e.g., amino acids and vitamins), recombinant products (e.g., recombinant yeast-expressed human Insulin), or are derived from bovine material obtained from U.S. or Canadian sources (considered BSE/TSE-free). The cell culture medium contains three bovine products: bovine serum albumin (BSA), transferrin, and lipoprotein fractions.

There are two parts to the fermentation process - T-Flask and spinner culture in which the volume (and number of cells) of the WCB is increased, and the larger-scale bioreactor process where the cell culture volume is increased incrementally to the final volume of 10,000 liters or more. At the start of each production run, a vial containing about 10 million frozen cells from the Working Cell Bank (WCB) is thawed and expanded through a series of flasks and bioreactors filled with cell culture media. The

NS0 myeloma cells continuously secrete the palivizumab monoclonal antibody into the liquid medium throughout the fermentation process. About 18-22 days after inoculation of the production bioreactor, the cells and debris are removed and the pH and conductivity of the resulting cell-free conditioned media are adjusted for further processing and purification.

The first step in purification is microfiltration through a membrane that blocks large materials such as myeloma cells and debris but allows passage of proteins, such as antibodies, and other solubilized substances. The palivizumab is purified from the liquid phase via three-stage chromatography, acid treatment, and nanofiltration to remove process contaminants such as viruses, bovine serum albumin, transferrin, and endotoxin. The final product is formulated by stabilization at pH 6.0 with histidine, glycine, and mannitol. Bulk Synagis is passed through a 0.22 micron filter and filled in glass vials. The resulting sterile product is then lyophilized (freeze-dried). Every lot is validated for purity, potency and sterility. The palivizumab purification process includes several (unspecified) virus removal/inactivation steps (probably referring to nano-filtration, acid treatment and, perhaps, the chromatography steps). In-process controls include testing of samples for fill volume and integrity testing of sterilization filters. Validation is performed according to standard procedures. Viral clearance studies are conducted throughout the Synagis manufacturing operation.

Benzonase, a recombinant endonuclease from *Serratia marcescens* manufactured in transformed *Escherichia coli* (*E. coli*), is used in the manufacture of palivizumab. The product was developed and patented (e.g., U.S. 5,173,418) by Benzon Pharma A/S,, with NycoMed Pharma A/S holding worldwide patent rights. The product is manufactured, and exclusively distributed for commercial use by Merck KgaA under (sub)license from NycoMed (under license from Benzon). In Jan. 2007, Merck KGaA acquired Serono, and the new company was renamed Merck Serono S.A. This promiscuous endonuclease attacks and degrades all forms of DNA and RNA (single stranded, double stranded, linear and circular), and is effective over a wide range of operating conditions. Benzonase is used to break down and remove residual polynucleotides (DNA and RNA) after cell culture. FDA has granted Benzonase a type II Drug Master File (DMF #BBMF 5403). MedImmune may not have formally licensed Benzonase, rather those purchasing commercial quantities may automatically/implicitly receiving a license for its use.

Routine testing on the finished product includes appearance of the lyophilized powder and reconstituted solution, pH, moisture, total protein, biological potency, identity, size exclusion chromatography, endotoxins, sterility, and uniformity of content. SDS PAGE and RSV Microneutralization assays have been validated and are used for quality control. Palivizumab reference standards have been developed. The characterization of the reference standard includes a series of analytical tests to confirm that its structural identity and biological activity are consistent with the set criteria.

During the course of Phase I through III trials, palivizumab was manufactured by MedImmune in various bioreactor sizes including 20, 45, 100, and 200 liters. This was further scaled-up and three consistency lots were manufactured by MedImmune in 500 liter bioreactors. Combined data from 20-500 liter lots were used to support

approval. Boehringer Ingelheim further scaled-up the process from 400 to 10,000 liter bioreactors, and testing showed materials produced by both companies and all lot sizes were comparable using a variety of analytical methods [see "Comparability Testing of a Humanized Monoclonal Antibody (Synagis) to Support Cell Line Stability, Process Validation, and Scale-Up for Manufacturing," *Biologicals*, 27, p. 203-15, 1999].

All stages of antibody production by Boehringer Ingelheim from cell culture to harvesting, purification, formulation, filling and lyophilisation are performed at its facilities in Biberach, Germany.

Medium components include synthetic chemicals (e.g., amino acids), recombinant human Insulin, and some bovine-derived materials (e.g., BSA, transferrin, lipoprotein fraction) made from plasma sourced in U.S./ or Canada and are free of BSE

Recombinant protein reexpression using technology from Cambridge Antibody Technologies, Inc. (now MedImmune Cambridge, another Astra Zeneca subsidiary) are attributed as improving MedImmune's productivity for Synagis manufacture to 3-4 g per liter..

**FDA class:** Biologic BLA

**CBER class:** Viral And Rickettsial Vaccines

**CBER to CDER:** Among the products transferred within FDA on June 30, 2003

**Approvals:** Date = 19980619; first approval; BLA 97-1359; for product manufactured at MedImmune's Gaithersburg, MD, facility

Date = 19990908; BLA supplement; Indication = approval of manufacture by Boehringer Ingelheim Pharma KG under contract to MedImmune

Date = 19991217; BLA supplement; Indication = approval of manufacture at MedImmune's new facilities in Frederick, MD, to augment product manufactured by Boehringer Ingelheim. The approval acknowledged the therapeutic and other equivalence of palivizumab produced by MedImmune and Boehringer Ingelheim.

Date = 20010000 (sometime in 2001); Indication = approval for manufacture using "Enhanced Yield Process" (EYP), which improves Synagis fermentation yields by over 300%

Date = 20030916; BLA supplement; Indication = addition to product insert/labeling of findings supporting use in young children with hemodynamically significant congenital heart disease (CHD) to prevent hospitalization caused by RSV.

Date = 20040724; BLA supplement; Indication = new liquid formulation

**Indications:** [full text of "INDICATIONS AND USAGE" section from product insert/labeling]:

Synagis (palivizumab) is indicated for the prevention of serious lower respiratory tract disease caused by respiratory syncytial virus (RSV) in pediatric patients at high risk of RSV disease. Safety and efficacy were established in infants with bronchopulmonary dysplasia (BPD) and infants with a history of prematurity ( $\leq 35$  weeks gestational age). (See Clinical Studies section).

**Status:** The BLA was filed on Dec. 19, 1997, received priority review, and was approved by FDA on June 19, 1998; an on-target approval time of six months (0.5 year). Product sales began on September 15, 1998. This allowed for production and product launch in time for the fall 1998 RSV season in the U.S. The FDA approved Synagis without the usual review and recommendation by an advisory committee, in this case the Vaccines and Related Biological Products Advisory Committee.

Synagis was approved on August 13, 1999 in the European Union (EU) "For the prevention of serious lower respiratory tract disease requiring hospitalization as caused by respiratory syncytial virus (RSV) in children who are born at 35 weeks of gestation or less and were less than 6 months of age at the onset of the RSV season, or in children who are less than 2 years of age and had required treatment for bronchopulmonary dysplasia within the last 6 months." On Oct. 30, 2003, EU supplemental approval was granted "for use in infants less than two years of age born with hemodynamically significant congenital heart disease (CHD) to prevent serious lower respiratory tract infection (LRTI) hospitalisation caused by respiratory syncytial virus (RSV)."

On July 2004, a new liquid formulation was approved. This offers improved convenience. The lyophilized formulation requires reconstitution with sterile water, a process that takes ~20 minutes, and the product must be used within the next six hours. MedImmune plans to end production of the lyophilized formulation for the U.S. on October 2004, and to begin manufacturing liquid Synagis, which is expected to be launched later in the U.S. later in 2004, in time for the 2005-2006 RSV season.

**Tech. transfer:** U.S. patent, 5,824,307, "Human-murine chimeric antibodies against respiratory syncytial virus," Oct. 20, 1998, assigned to MedImmune, Inc., covers palivizumab (see also EP 0783525). This composition of matter patent protects Synagis through October 20, 2015. The official abstract states: "This invention relates to a human antibody which contains the one CDR from each variable heavy and variable light chain of at least one murine monoclonal antibody, against respiratory syncytial virus which is MAb1129 and the use thereof for the prevention and/or treatment of RSV infection." The exemplary claim (no. 1) states, "A neutralizing antibody against RSV, comprising: a human constant region and a variable region, said variable region comprising heavy and light chain framework regions and heavy and light chain CDRs, at least a portion of the heavy and light chain framework regions being derived from a human antibody, said neutralizing antibody against respiratory syncytial virus binding to the same epitope as an antibody comprising three heavy chain CDRs comprising amino acids 31-37, 52-67 and 100-109 of SEQ ID

NO:31, and three light-chain CDRs comprising amino acids 24-33, 51-56 and 89-96 of SEQ ID NO:3." Additional patent applications which could provide even broader and longer protection are pending. [DataMonitor and ABN Amro report that U.S. patent protection for Synagis expires in 2004, but this is wrong].

Antibody humanization design/construction technology for palivizumab has also been nonexclusively licensed by MedImmune from Protein Design Labs. (PDL). Based on a Jan. 2003 CIBC World Markets Report on PDL, the company receives royalties of 2.85%, a rate similar to what the company receives from other licensed manufacturers of humanized Mabs. The basic technology for PDL's antibody humanization is disclosed by Queen, et al., in 5,530,101 and related patents and Winter, et al., in U.S. patent 5,225,539 and related patents. See the Tech. transfer (rDNA) section of the Monoclonal Antibodies entry (#300) for further information.

In June 2005, the U.S Court of Appeals for the Federal Circuit upheld a lower federal court's decision that denied a suit brought by MedImmune against Johnson & Johnson (J&J) seeking declaratory judgment that Synagis does not infringe J&J's Centocor subsidiary's U.S. patent 5,807,715 concerning chimeric antibodies and antibody fragments.

Manufacture of palivizumab entails use of the glutamine synthetase (GS) recombinant mammalian cell selection, amplification and expression system developed by Celltech Biologics plc, now Lonza Biologics plc, a subsidiary of Alusuisse-Lonza Group. Lonza Biologics receives unspecified royalties from MedImmune on sales of Synagis from licensing of its patents covering the GS gene expression system. GS technology involves dominant selectable markers for use in amplification of genes and transforming host cell lines to glutamine independence. See related patents including U.S. 5,770,359 and 5,747,308. The technology is coassigned to the University of Glasgow. The glutamine synthetase gene is used in recombinant vectors as a marker along with (an)other desired gene(s) for expression, with only successfully transformed mammalian cells (normally deficient in glutamine synthetase) being capable of producing their own GS and surviving in glutamine-deficient culture media. Over forty companies have licensed GS System technology for various uses.

MedImmune negotiated a Biological Materials License (BML) from the National Institutes of Health (NIH) for an unspecified biological material. Molecular Vaccines, Inc., now MedImmune, in the early 1990s also nonexclusively licensed U.S. 4,800,078, invented by researchers with the National Institute of Allergy and Infectious Diseases (NIAID), NIH. This license is no longer active. The patent's single claim concerns RSV monoclonal antibodies and immune globulins delivered by inhalation aerosol (while Synagis is administered by intramuscular injection).

Cabilly-Boss/Cabilly II Dispute: See the Monoclonal Antibodies entry (#300) for further background about patents originally granted to Genentech (Cabilly) and Celltech (Boss) broadly covering aspects of humanized recombinant monoclonal antibodies. Through a complex series of events, including Genentech acquiring the Boss patent portfolio from Celltech and Genentech recently receiving a new patent (Cabilly II) essentially combining the claims from the previously-issued Cabilly and Boss patents,

Genentech now holds technology that nearly all companies planning to manufacture recombinant monoclonal antibodies must license, with Cabilly II being very controversial and challenged by multiple companies, with MedImmune very prominent among these in connection with its having licensed Cabilly-Boss technology from Genentech for use with Synagis.

In Oct. 2000, Celltech Chiroscience Ltd., now Celltech Group plc, filed a suit in the U.K. alleging that MedImmune failed to pay royalties on sales of Synagis as required by a license agreement MedImmune had concluded in Jan. 1998. Subsequently, with Genentech's "New Cabilly" patent and the cross-licensing between Celltech and Genentech, Genentech is now demanding royalties from MedImmune on sales of Synagis. However, with the subsequent combining of the Boss and Cabilly patents (New Cabilly) and the related significant extension of U.S. patent coverage for essentially the same technology, MedImmune is challenging the the validity of New Cabilly.

MedImmune never paid royalties to Celltech under its 1998 licensing agreement, and in Jan. 2004 filed a challenge to validity of the Boss patent. Celltech filed a countersuit seeking royalties based on U.S. sales of Synagis in March 2004. In June 2005, MedImmune reached a settlement with Celltech regarding royalty payments due under its original license agreement. MedImmune will pay unspecified royalties to Celltech. This does not settle MedImmune's ongoing dispute with Genentech over the New Cabilly patent.

MedImmune, Inc. responded to the Genentech-Celltech cross-licensing of the Boss and Cabilly patents by filing suits in federal court alleging antitrust violations between Genentech and Celltech, and challenging the "New Cabilly" or "Cabilly II" patent (6,331,415). MedImmune alleged that Genentech and Celltech conspired to gain a monopoly, with Celltech agreeing to abandon defense of its 2006-expiring Boss patent in exchange for continuing (through 2018) to receive (cross)licensing revenue from Genentech's licensing of its New Cabilly patent and access (through cross-licensing) to the New Cabilly patent for its own products. MedImmune asserted that the Genentech-Celltech agreement resulted in 29 years of patent protection for the same technology. In May 2004, a U.S. District Court dismissed MedImmune's suit, with the Genentech/Celltech patents and agreements remaining intact. The judge ruled in favor of Genentech, because a U.S. District Court judge had previously approved the Genentech-Celltech agreement. Challenges to 6,331,415 ("New Cabilly") have not been resolved yet.

In Jan. 1998, MedImmune licensed Celltech's Boss patent for use with Synagis. Under this agreement, MedImmune obtained a worldwide license to Celltech's "Boss" patent (and related applications) concerning recombinant chimeric/humanized monoclonal antibody co-expression technology. The situation concerning recombinant monoclonal antibody patents, licensing, cross-licensing and disputes is very complex. This included an extended patent dispute between Genentech and Celltech Group (being acquired by UCB Bioproducts in mid-2004) concerning their respective patents covering basic recombinant monoclonal antibody design and expression technologies. See the "Tech. transfer (rDNA)" section of the Monoclonal Antibodies entry (#300) for

further information.

Celltech received its "Boss" U.S. patent (expiration in 2006) and Genentech received its original "Cabilly" U.S. patent (expiration in 2006), both on the same day. Celltech's Boss patent was later revoked; and Genentech later received its "New Cabilly" patent (6,331,415; expiration in 2018), including claims copied from the revoked Celltech "Boss" patent. Genentech and Celltech later settled their disputes and cross-licensed their patents, with Genentech taking the lead in licensing. As a result, in many respects, Celltech's U.S. "Boss" patent (licensed by MedImmune for Synagis) was broadened and its expiration extended by over a decade, from 2006 to 2018. MedImmune filed challenges with the patent office and in federal court seeking to invalidate New Cabilly and is accusing Genentech and Celltech of monopoly-related restraint of trade. These cases have yet to be resolved.

Analysts report that MedImmune paid Genentech about \$30 million in royalties for its Cabilly-Boss license in 2005.

In fall 2006, the U.S. Supreme Court considered a suit (MedImmune v. Genentech) filed by MedImmune seeking to end its payment of Cabilly-related royalties to Genentech. The court was asked to rule whether MedImmune has the right contest its licensing agreement and challenge the validity of the Cabilly II patent held by Genentech without first being in breach of its licensing agreement with Genentech. This would decide and set a precedent for whether a patent licensee has to refuse to pay royalties or otherwise be in material breach of its license agreement before it can sue to have a licensed patent declared invalid, unenforceable or not infringed. MedImmune was and is a paid-up licensee, but has made its payments to Genentech with formal protests. Breaching the contract would automatically result in punitive fees and revocation of the license, which MedImmune sought to avoid. The Supreme Court only considered the threshold standing issue (right to challenge a licensed patent without being in violation of the licensing agreement) and did not review the validity of the Cabilly II patent. As explained by MedImmune regarding the ruling of the lower court that was being appealed, "The Federal Circuit has effectively ended actions by patent licensees to challenge patents, unless those licensees first place themselves in breach, and consequently in jeopardy of license termination, substantial liability and penalties." The Federal Circuit court had rejected the view that licensee rights established under *Lear v. Atkins*, 395 U.S. 653 (1969), permit a patent validity challenge, stating that this case is governed not by the bar against licensee estoppel, but by the Constitution's requirement of a case or actual controversy, i.e., that a current licensee has no standing to sue for declaratory judgment, because there is no immediate threat of being sued for patent infringement. A license agreement has generally been thought of as a settlement of a dispute. If MedImmune were upheld, however, patent related to an ongoing license agreement could be subject to litigation between the licensee and licensor.

On Sept. 5, 2006, the Supreme Court ruled in MedImmune v. Genentech. See the Tech. transfer section of the Monoclonal Antibodies entry (#300) for further information. Essentially, MedImmune won the right to continue to contest Cabilly II patent in federal courts, with the Supreme Court ruling that companies can challenge

licensed patents even if they are currently in good standing, in terms of their licensing contract.

In 2007, the U.S. Patent and Trademark Office is continuing its review of Genentech's Cabilly patent under concurrent proceedings for an Inter Partes Reexamination (RE Appl. No. 90/007,542) and an Ex Parte Reexamination (RE Appl. No. 90/007,859).

**Trials:** In cotton rat experiments, palivizumab achieved a mean reduction in pulmonary RSV titer of 99% at serum levels of 25-30  $\mu$ g/mL, and all animals with serum levels above 40  $\mu$ g/mL had at least a 2log10 reduction in pulmonary RSV titer (Johnson 1997). A serum level of 30-40 mg/mL was used as the minimum target trough for subsequent clinical trials of palivizumab, corresponding to a monthly intramuscular (IM) dose of 15 mg/kg. The increased potency of palivizumab compared to RSV-IGIV (RespiGam) permitted a 50-fold reduction in dose in infants.

In IMPact-RSV, the first pivotal Phase III placebo-controlled efficacy trial in at-risk infants (those with bronchopulmonary disease up to 24 months of age or with a history of prematurity up to 6 months of age), 1502 children were randomized in a multi-center, parallel group, placebo-controlled study that evaluated the safety and efficacy of palivizumab in preventing hospitalizations related to RSV infection. In addition, a second pivotal Phase 3 study (CP048) evaluated children up to 24 months of age with hemodynamically significant congenital heart disease. In these two studies, ~50% of the palivizumab treated children were spared hospitalizations for lower respiratory tract disease due to RSV, the complications of a severe disease course and the stress of subsequent treatment regimen. These efficacy data for palivizumab plus safety data at 15 mg/kg IM indicate that palivizumab is safe and well tolerated and has shown proven efficacy in the currently approved indication that is the prevention of serious lower respiratory tract disease caused by RSV in children at high-risk of RSV disease.

**Medical:** The recommended dosage is 15 mg/kg (with palivizumab containing 100 mg/ml) administered once monthly throughout the RSV season (generally Nov.-April). The first dose is best administered starting prior to commencement of the RSV season, generally in the fall and winter months, but the season may begin earlier or persist later in certain communities. The safety and efficacy of Synagis have not been demonstrated for treatment of established (chronic) RSV disease.

**Disease:** RSV is a common disease among infants and children, but can be particularly harmful, including causing death, in infants born prematurely or with underlying respiratory disease (bronchopulmonary disorders). RSV is responsible for the largest proportion of respiratory infections in infants and children. Because premature birth interrupts the final stages of fetal development, each premature infant is at risk for contracting serious RSV disease, such as bronchiolitis or pneumonia due to RSV. Premature infants do not have a normal immune response or the lung capacity of full-term children to resist lower respiratory tract infections. Recent data indicate that compared to normal birth weight children, those born at a low birth weight are five times as likely to die with bronchiolitis. The risk of serious RSV infection and hospitalization increases with risk factors such as premature birth, chronic lung disease, congenital heart disease, low birthweight, passive smoke exposure, daycare

attendance, multiple birth, family history of asthma, and birth within six months of the onset of RSV season.

RSV is generally transmissible by direct or close contact, probably inhalation of respiratory aerosol droplets. RSV can live on tissues and surfaces, e.g., counter tops, for 4 to 7 hours, and the virus can survive on the hands for about 0.5 hour. Nosocomial (hospital-associated) infections are common in infants and medical staff. The incubation period for RSV disease (respiratory symptoms) is 2-8 days. Live virus is usually shed for about 3-8 days, but this may last 3-4 weeks in infected infants with low or no neutralizing antibody titers. Infants born premature and others with suppressed immune systems are particularly susceptible to RSV infection.

An estimated one-third of the 12.2 million respiratory infections that occur in children under age five is attributed to RSV. Half of all children develop RSV infection by the age of one year and, by the age of two, virtually all children have been infected. For most otherwise healthy children over age four, RSV usually amounts to little more than a cold. In children under age four, it can cause lower respiratory tract infection. Most RSV infections start with a low-grade fever, a runny nose, and cough, which may be accompanied by difficulty in breathing and wheezing. The infection may last as long as two to three weeks.

A small percentage of infants and children who contract RSV are at high-risk for hospitalization, particularly premature infants and others with bronchopulmonary disorders. The largest proportion of Synagis is used for treatment of infants born prematurely.

RSV is the most common cause of lower respiratory tract infection in children under five years of age and the number one reason for hospitalization of children under the age of one. The Centers for Disease Control and Prevention (CDC) now estimates that each year up to 125,000 children under the age of five are hospitalized with serious RSV disease (primarily during the RSV season - from fall through spring). Only a few years ago, about 4,500 deaths annually are attributed to the disease. An article in the October 20, 1999 issue of the Journal of the American Medical Association reported that an increasing number of children in the U.S. are being hospitalized for bronchiolitis, often caused by RSV infection, with over half of hospitalizations among infants under six months of age and 81% among those under 1 year old. Between 1980 and 1996, there were an estimated 1.65 million hospitalizations for bronchiolitis among children under age five, for a total of seven million in-patient days.

The rate of births of premature babies is on the rise, providing a growing market for Synagis. Between 1981 and 2001, the annual rate of premature births rose more than 27% (from 9.4% to 11.0%). Prematurity now affects one out of every eight babies. In an average week in the U.S., there are 9,159 babies born before the 37th week of gestation and 1,493 babies are born at less than 32 weeks of gestation.

Blacks and Hispanics in the U.S. both have high rates of premature and low birth weight babies. However, despite the increased risk for RSV, many mothers do not

know about RSV. A recent survey conducted by Harris Interactive found that nearly 90% of Black and Hispanic mothers were not aware that RSV is a serious infectious illness that affects infants and young children. Even fewer knew that RSV could put babies with risk factors such as prematurity, low birth weight, or daycare attendance at risk for hospitalization, or worse.

Congenital heart defects are structural problems of the heart that are present at birth, having occurred during development. About 32,000 children are born in the U.S. each year with CHD, of which there are many different types with varying degrees of severity. Children born with serious CHD who have decreased cardiac or pulmonary reserve are at highest risk of serious RSV infection. These children require intensive care and use mechanical ventilation with RSV infection more frequently than children who do not have CHD. Further, children with CHD who are hospitalized with RSV have a fatality rate that is 2-6 times greater than those having RSV without CHD. Synagis is an important preventative option for children with significant CHD.

**Market:** Worldwide 2007 revenues from sales of Synagis by MedImmune (including sales to Abbott) were \$1.146 (according to IMS).

Total world-wide sales by MedImmune (including sales to Abbott) were \$1.065 billion in 2006, \$1.063 billion in 2005 (achieving blockbuster status); \$943.0 million in 2004 (\$987 million for the 2004/2005 RSV season); \$848.8 in 2003; \$668 million in 2002, \$516.4 million in 2001, \$427 million in 2000, \$352 million for the 1999/2000 RSV season (essentially all sales in 1999), and \$227 million for the 1998/1999 season (sales in 1998. Ex-U.S. revenue was \$158 million in 2005, and \$72 million in 2003.

Total 2006 sales by Abbott have been estimated to be about \$115 million (only about half a year), and \$130 million in 2005.

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For 2007 total sales, a "consensus" Wall Street analyst projection had been reported to be \$1.48 billion.

Friedman Billings and Ramsey (FBR) have projected (4/2007) total Synagis revenue of \$1.065 billion in 2006, \$1.106 billion in 2007, \$1.229 billion in 2008, and \$1.120 million in 2009 (with MEDI-524 entering the market) and \$839.2 million in 2010. Total U.S. sales (by MedImmune) are projected to be (or have been) \$905.0 million in 2005, \$905.4 million in 2006, \$1.023 billion in 2007, \$1.054 billion in 2008, \$960.2 million in 2009, and \$694 million in 2010. MEDI-524, Synagis' replacement, is projected to enter the market in 2009, with \$221.8 million sales in 2009 and \$559 million in 2010.

In Dec. 2005, MedImmune reported, "to date, Synagis has been used to protect more than 700,000 infants in the United States from RSV."

The 2005 Average Wholesale Price (AWP) is \$885.40/50 mg vial; and \$1,671.88/100

mg vial (Red Book, 2007). \*\*TAB

TAB\*\*MedImmune reported that Synagis provided an ~17%-25% cost savings compared to RespiGam, which it replaced, including the cost of administration of i.v. fluids, infusion pump, and nursing time.

During the 2003/2004 RSV season, an average of 4.1 doses were administered to each treated infant, with this in line with prior use and showing that new dosing guidelines from the American Academy of Pediatrics (AAP) recommending limiting use to five doses had not significantly affected use of the product.

The launch of Synagis in the 1998/1999 RSV season was the most successful introduction of any biopharmaceutical product to date. MedImmune estimates that Synagis was used in its first season in the U.S. by 15 to 20% of the children who could potentially benefit from its use. Over 150,000 infants received Synagis from its launch in Sept. 1998 through the 1999/2000 RSV season.

Synagis is now a mature product, with annual growth leveling off to about about 10% or less. With few RSV treatments in the pipeline, its only real competition will be from motavizumab from MedImmune, which is expected to replace Synagis. Several small molecule drugs are being developed for RSV treatment, but these may end up being used in addition to Synagis or Numax.

In mid-2006, with the end of marketing by Abbott, MedImmune is expanding its sales force with hiring of 125 sales reps.

**Competition:** Synagis has largely replaced blood plasma-derived Respiratory Syncytial Virus Immune Globulin (RespiGam; entry #781) from MedImmune. Synagis offers a number of advantages over RespiGam. A major advance is that Synagis can be administered by simple intramuscular (IM) injection vs. 2-4 hour intravenous infusion.. Besides the improved safety offered by a recombinant vs. a blood-derived product, Synagis offers improved convenience, requiring only about 1 mL/dose which is administered by simple intramuscular injection, while RespiGam requires 100 mL/dose and intravenous infusion over a four-hour period. For MedImmune, Synagis offers higher profit margins, e.g., the Cost of Goods (COG; manufacturing cost) for RespiGam, which is manufactured by another organization, has been reported to be about 50% while the COG for Synagis is about 10%.

Synagis currently has little or no real competition. Aerosolized ribavirin (Virazole) from Ribapharm, a subsidiary of ICN Pharmaceuticals, is marketed in the U.S. for treatment (not prevention) of infant RSV infection, but its use is limited by the prolonged aerosol administration required and safety concerns including potential exposure of pregnant women to ribavirin. No vaccines are available for prevention of RSV.

**Ongoing.:** See the entry below for motavizumab (NuMax), which is expected to replace this product.

MedImmune concluded an agreement with Alkermes Inc. in June 2000 for the

development and licensing of inhaled formulations of palivizumab (or NuMax) using its AIR pulmonary delivery technology. However, this has not been tested in clinical trials, and MedImmune is concentrating on injectable NuMax.

Researchers from MedImmune reported results from a preclinical study of an intranasal bivalent recombinant respiratory syncytial virus (RSV) and parainfluenza virus type-3 (PIV-3) prophylactic vaccine in the Oct. 2004 issue of the Journal of Virology, with a protective immune response observed in monkeys against both viruses. The vaccine involves recombinant PIV-3 also presenting RSV F (fusion) protein. The vaccine entered Phase I trials in late 2004. MedImmune has entered into a Cooperative Research and Development Agreement (CRADA) with the National Institute of Allergy and Infectious Diseases (NIAID), NIH, for PIV-3/RSV vaccine development. The company is also developing a vaccine against human metapneumovirus (hMPV), a source of serious lower respiratory tract infections in young children, and will likely combine this with its PIV-3/RSV vaccine.

In Dec. 2005, MedImmune linked with Biota Holdings Ltd. (Melbourne, Australia) to develop and commercialize Biota's small molecule drugs for treatment of RSV infection. MedImmune holds worldwide marketing rights, except for Australia, New Zealand, China and Southeast Asia (including India and Pakistan).

**Nomenclature:**

RSV Mab1, rDNA [BIO]

Synagis [TR]

Palivizumab [FDA USAN INN]

MEDI-493 [SY]

respiratory syncytial virus (RSV) monoclonal antibody, humanized [SY]

60574-4111-01 [NDC]

**Annual sales (2007; \$million):** \$1146 ; BLOCKBUSTER! (sales >\$1 billion)

**FDA Class:** Biologic BLA

**Year of approval (FDA) = 1998**

**Date of 1st FDA approval = 19980619** (in format YYYYMMDD)

**Index Terms:**

o [Product Class Index:](#)

antibodies (see also immune globulins; monoclonal antibodies)

biopharmaceutical products

blockbuster sales (over \$1 billion/year)

bovine materials used<!-- bovinesource -->

expression, mammalian

human materials used<!-- humansource -->

monoclonal antibodies, recombinant

murine (mouse) materials used

recombinant DNA

yeast source materials

yeast source materials

SB001 BIOPHARMA prod. (mainstream)

- [Regulatory/Status Index:](#)

EU200 Currently Approved in EU  
UM001 Marketed Product in US  
US200 Currently Approved in US  
EM001 Marketed Product in EU

- [Biological Index:](#)

albumin, bovine serum  
Benzonase  
bioreactors, 10,000 Liter  
bioreactors, spinner culture  
bovine lipoproteins  
bovine serum albumin (BSA)  
bovine transferrin  
fed-batch system  
glutamine synthetase (GS) expression system  
insulin, recombinant human  
Mab 1129, murine monoclonal antibody  
mammalian cell culture  
monkey cells<!-- monkeycells -->  
murine myeloma cells  
NS0 mammalian cell line  
respiratory syncytial virus (RSV) fusion (F) protein  
stirred-tank, fed-batch system  
T-Flask culture  
transferrin, bovine

- [Chemical Index:](#)

Benzonase  
glycine  
histidine  
lyophilized (freeze-dried)  
monoclonal antibody, Mab 1129  
nuclease, Benzonase  
Sterile Water for Injection  
viral inactivation, unspecified