

Record Number of Biopharmaceuticals Approved

2005 Was a Record-Setting Year

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This past year, the FDA broke its own record for biopharmaceutical approvals. Twenty one biopharma-

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ceutical products received original FDA approval in 2005. There were 15 FDA approvals in 2004, 20 in 2003, 13 in 2002, 11 in 2001, and 12 in 2000.

Biopharmaceutical product approvals from January 1, 2005, to July 1, 2006, are summarized in the *Table*.

So far in 2006, product approvals are off to mediocre start. Seven products received original FDA approval in the first half of 2006. If approvals continue at this rate, 2006 will be a relatively slow year compared to the approvals in 2005. These data are included in the new 5th edition of "Biopharmaceutical Products in the U.S. and European Markets."

New Biopharmaceutical Entities in 2006

New biopharmaceutical entities (NBEs) are defined as products involving novel biopharmaceutical active ingredients not substantially similar to previously approved products. These new products usually have active ingredients with novel identity/sources, methods of manufacture,

and specifications. Five of the seven first-half 2006 approvals were NBEs.

· **Gardasil**, an HPV vaccine from **Merck** (www.merck.com), has been widely hailed as the first vaccine for prevention of oncogenic virus-associated cancer, in this case cervical cancer (but many consider hepatitis B virus vaccines, which first became available in the 1980s, to be the first vaccines for cancer prophylaxis, in this case hepatocarcinoma).

Gardasil is a quadrivalent (tetraivalent; four antigen) human HPV vaccine containing recombinant HPV L1 protein virus-like particles from HPV types 6, 11, 16, and 18 expressed by a transformed *Saccharomyces cerevisiae* (yeast) cell line complexed with a conventional aluminum adjuvant.

This range of HPV antigens is designed to provide protection against most cervical cancer (primarily due to HPV types 16 and 18) and genital warts (primarily due to HPV types 6 and 11). This vaccine is optimally used in prepubescent females (and also males) before HPV-infection due to sexual activity. It will be interesting to see how Merck markets this vaccine, as many social conservatives are against required pediatric use, alleging that this would encourage sexual promiscuity.

· **Myozyme**, from **Genzyme** (www.genzyme.com), is a formulation of recombinant glycosylated alpha glucosidase enzyme, which degrades glycogen, expressed by CHO cells. Myozyme is the first treatment available for patients with Pompe disease, a lysosomal storage disease

involving accumulation of incompletely degraded glycogen in the lysosomes of cells

· **RotaTeq**, a rotavirus vaccine from Merck, is a formulation of five live bovine/human reassortant (natural recombinant) rotavirus strains cultured in VERO cells, a continuous African green monkey kidney cell line, used as an oral vaccine for prevention of pediatric rotavirus disease. Another rotavirus vaccine, **RotaShield** from **Wyeth** (www.wyeth.com), previously received FDA approval, but was composed of fully human reassortant virus and was taken off the market due to rare, but serious, adverse effects

· **Pfizer's** (www.pfizer.com) **Exubera** is an inhalable dry powder, rapid-acting formulation of recombinant insulin expressed by transformed *E. coli* bacteria stabilized in ~1-micron glass-stabilized particles using mannitol as an inert amorphous glass-like matrix. The insulin is essentially the same as in other nonmodified insulin products, but the modification of insulin by physical encapsulation confers substantially different pharmacokinetic properties.

· **Lucentis** from **Genentech** (www.gene.com) is a recombinant Fab fragment of a humanized murine monoclonal antibody expressed in *E. coli* bacteria with binding specificity for vascular endothelial growth factor (VEGF).

Lucentis is an anti-angiogenesis agent and reportedly the first therapeutic with the ability to reverse wet, the most common type, of age-related macular degeneration (AMD).

Genentech has priced this at nearly \$2,000/vial or injection (>\$10,000/year). However, one of Genentech's own products, **Avastin**, a full-sized recombinant

VEGF monoclonal antibody approved for cancer treatment, may cannibalize sales of Lucentis. Anecdotal reports involving thousands of patients treated with low-dose Avastin, costing <\$20/dose, indicate that this is also safe and effective for wet AMD. Genentech has no plans to test and seek approval of Avastin for wet AMD. It remains to be seen whether physicians and insurers, potentially facing liability and malpractice suits, will use Lucentis or adopt cheaper Avastin off-label.

Less Novel Biopharmaceuticals in 2006

A major goal for biopharmaceutical development has always been the introduction of improved products. These products have active agents with substantial similarities to previously approved products.

- Omnitrope from Sandoz, the generics subsidiary of **Novartis** (www.novartis.com), has been widely reported to be the first FDA approval of a biopharmaceutical as a generic drug, but it is simply the first widely publicized case and sets no precedents.

Omnitrope contains recombinant somatotropin (human growth hormone) expressed by transformed *E. coli* bacteria, similar to six other somatotropin products already in the U.S. market.

- Zostavax, from Merck, is the first vaccine for prevention of herpes zoster (shingles), a disease common in older adults caused by reactivation of latent varicella-zoster virus (VZV) infection. Similar to Varivax, Merck's current pediatric chickenpox vaccine, Zostavax is a formulation of live attenuated VZV Oka/Merck strain cultured in MRC-5 human diploid fibroblast cells, with Zostavax having a higher viral titer.

- HepaGam B from **Cangene** (www.cangene.com) is a formulation of purified gamma globulin fraction isolated from human plasma containing polyclonal antibodies to hepatitis B virus surface antigen. A substantially similar product, Nabi-HB, manufactured by Cangene for marketing in the U.S. by **Nabi** (www.nabi.com), had previously received approval. This product from Cangene now essentially replaces Nabi-HB.

NBEs in 2005

Among the eight 2005 NBEs (represented by nine new products), four are fully or truly novel, in the sense of not being substantially similar to prior products, with two of these genetically engineered to be novel and one a combination vaccine containing novel conjugate immunogens.

- Orenzia from **Bristol-Myers Squibb** (BMS; www.bms.com), approved for treatment of rheumatoid arthritis, is a recombinant fusion protein involving two human proteins fused together—two identical portions of cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4; a T-cell antigen for immune cell activation) linked to a portion of IgG.

- Levemir, from **Novo Nordisk** (www.novonordisk.com), is a recombinant mutein (analog) of *Saccharomyces cerevisiae*-expressed human insulin with a modified amino acid sequence. This makes metabolic break-down of the molecule more difficult, making this a longer-acting form of insulin, according to the company.

- Menactra, a quadravalent (4-immunogen) vaccine against bacterial meningitis from **Sanofi Pasteur** (www.sanofipasteur.com), is reportedly the world's first quadrivalent conjugate vaccine. Menactra contains a combination of

individually cultured, inactivated, purified *Neisseria meningitidis* types A, C, Y, and W-135 capsular polysaccharides, similar to prior vaccines, but with each chemically conjugated to a diphtheria toxoid (inactivated *Corynebacterium diphtheriae* toxin) carrier. Conjugation increases the immunogenicity of the polysaccharides, resulting in longer protection than prior unconjugated polysaccharide vaccines, due to induction of T-cell-dependent immune responses.

Two 2005 NBEs are recombinant versions of human proteins, each previously unavailable in any form for therapeutic use.

- IPLEX, an insulin-like growth factor from **Insmad** (www.insmad.com), is a recombinant version of a naturally occurring complex of insulin-like growth factor-1 (IGF-1)

- Increlex, insulin-like growth factor-1 from **Tercica** (www.tercia.com), partnered with Genentech, is a recombinant version of a naturally occurring, uncomplexed insulin-like growth factor-1 (IGF-1).

Both IPLEX and Increlex became the first IGF-1-based therapeutics available for treatment of pediatric growth failure, providing an alternative to recombinant somatotropin for some patients.

Two NBEs (representing three products) are recombinant analogs of animal-derived or synthetic active agents in currently marketed products. These include new recombinant versions of a human enzyme and a hormone.

- Fortical, a nasal spray containing recombinant *E. coli* bacteria-expressed calcitonin from **Unigene Labs** (www.unigene.com), is the first recombinant form of the hormone calcitonin to receive approval.

- Hyaluronidase is the active enzyme in two different products, Hylenex (for injec-

tion) and Cumulase (for in vitro fertilization). These became the first recombinant hyaluronidase products and will compete against comparable animal-derived products (including another product approved in 2005).

· Naglzyme from **BioMarin Pharmaceutical** (www.biomarinpharm.com) is recombinant human N-acetylgalactosamine 4-sulfatase (arylsulfatase B) expressed by transformed CHO cells used for treatment of mucopolysaccharidosis VI.

Less-Novel Biopharmaceuticals in 2005

Products approved in 2005 with active agents with substantial similarities to previously approved products include.

· GEM 21S growth-factor enhanced matrix from **BioMimetic Therapeutics** (www.biomimetics.com), marketed by **Osteohealth** (www.ostehealth.com), contains recombinant platelet-derived growth factor (rhPDGF-BB) expressed by mouse NS0 cells in a human bone powder matrix. This is similar to previously approved Regranex containing rhPDGF-BB alone (without bone matrix) manufactured by **Chiron** (www.chiron.com).

· Hydase from **PrimaPharm** (www.primapharm.net) contains ovine (sheep) hyaluronidase and is similar to Vitrase from **Amphastar Pharmaceuticals**, also approved in 2005, and other prior animal-derived hyaluronidase products.

· ProQuad, a measles, mumps, rubella, and varicella vaccine from Merck is a quadruple combination vaccine. This vaccine essentially adds the previously approved varicella virus vaccine, Varivax from Merck, to the triple combination M-M-R II from Merck.

· Fluarix, an influenza vaccine from GlaxoSmithKline, is a conventional inactivated influenza vaccine that has long been marketed in European countries. Fluarix is notable as the first FDA-approved biologic manufactured in Eastern Europe.

· Boostrix from GlaxoSmithKline, like Adacel, is an adult booster vaccine using components similar to the company's present tetanus toxoid, diphtheria toxoid, and acellular pertussis (DTaP) pediatric vaccine. Boostrix contains a novel tetanus toxoid component.

· Tetanus Toxoid Concentrate, manufactured by Chiron, is a tetanus toxoid, a chemically inactivated/detoxified *Clostridium tetani* (tetanus) toxin used as a vaccine immunogen, similar to prior tetanus toxoids. This product is used as a component of Boostrix.

· Adacel from Sanofi Pasteur, like Boostrix, is an adult booster form of the company's tetanus toxoid, diphtheria toxoid, and acellular pertussis pediatric vaccine.

· Gammagard Liquid is a liquid formulation of Gammagard previously available in solid powder form.

· Vaccinia Immune Globulin, intravenous products from both **Cangene** (www.cangene.com) and **DynPort** (www.dynport.com), received approval for addition to the U.S. biodefense stockpile. A less pure, intramuscularly administered product had previously been available.

Orphan Drug Approvals, 2005–mid 2006

Five products were approved with orphan designation.

· Myozyme from Genzyme was approved for treatment of Pompe disease.

· Both IPLEX and Increlex were

approved for treatment of pediatric growth failure.

· BioMarin's Naglazyme was approved as an enzyme replacement therapy for mucopolysaccharidosis VI (Maroteaux-Lamy syndrome; polydystrophic dwarfism).

· Vaccinia immune globulin, intravenous from DynPort (but not the comparable product from Cangene) was approved with orphan designation for treatment of serious complications from infection with vaccinia virus (the active agent in current smallpox vaccines).

Biodefense Approvals

Two new versions of vaccinia immune globulin received accelerated approval for addition to the nation's biodefense stockpile. Both of these products are much purer, intravenously administered forms of previous products administered intramuscularly. Similar in some respects to biogenerics, these were approved based on abbreviated clinical trials primarily using surrogate markers of efficacy against vaccinia virus infection (antibody neutralization), rather than testing clinical efficacy against actual life-threatening viral infection.

Efficacy trials with these products were largely impossible due to the small number of persons experiencing life-threatening vaccinia virus infections after smallpox vaccination. These were approved under animal rule guidelines, implemented specifically for biodefense products where full efficacy trials are often infeasible. Both were approved for biodefense stockpiling, and will not be marketed in the conventional sense.

Both are being manufactured under federal contracts, with the products being

stockpiled for emergency use (smallpox outbreak). In addition to the U.S. government, these and other biodefense biopharmaceuticals will find a ready and profitable export market.

Where are the Blockbusters?

Monoclonal antibodies—Despite a large number of recombinant monoclonal antibodies in development and considerable publicity, only one monoclonal antibody product was approved in 2005–to mid 2006—Abatacept from Bristol-Myers Squibb.

Cancer therapeutics—Although cancer has long been the indication/disease with the largest number of biopharmaceutical approvals and a large number of biopharmaceuticals in development, there were no biopharmaceutical approvals for cancer therapeutic indications in 2005–mid 2006.

Mainstream U.S. Biopharma Firms?

Established biopharmaceutical/biotechnology companies, such as **Amgen**, **Genentech**, **Biogen Idec**, are involved with few of the products approved in 2005–mid-2006. Most approvals involved either smaller, newer U.S. biopharma/biotech companies or large international, often foreign-based, pharmaceutical companies.

Biogeneric-like Approvals

Multiple 2005–mid-2006 approvals exhibited characteristics associated with approvals of generic biopharmaceuticals, such as biogenerics, follow-on proteins, follow-on biologics, biosimilars, and bio-comparables. These terms are generally applied to biopharmaceutical approvals involving active agents and formulations substantially similar, comparable, or iden-

tical to one or more already approved products, where the application process has been shortened/simplified, based on knowledge of one or more of the prior products.

This usually involves abbreviated trials, often just comparative bioequivalency studies with no large Phase III-type safety and efficacy trials and simplification of some chemistry, manufacturing, and control aspects of applications. FDA has yet to issue proposed regulations for either biogeneric drug or biologics approvals; and the U.S. biopharmaceutical industry has conflicted attitudes toward biogenerics.

FDA 2005–mid-2006 biogeneric-like approvals include recombinant somatropin (Omnitrope), recombinant calcitonin (Fortical), natural (Hydrase) and recombinant hyaluronidase (Hydrase, Hylenex, and Cumulase). These were all approved as drugs, not biologics, under section 505(b)(2), the same regulations used for approval of many generic small molecule and other drugs. Other simpler biopharmaceuticals regulated as drugs have been similarly approved in recent years.

With recombinant somatropin (human growth hormone) and calcitonin, the relative simplicity/smallness of these molecules makes them more closely resemble small molecule drugs than most biopharmaceuticals, thus allowing them to be considered within conventional generic drug evaluation/approval paradigms.

Most biopharmaceuticals involve proteins of much larger size with associated variations in 3-D structures. Many involve other structural modifications including glycosylation or attachment of carbohydrate strands, branching, cross-linking, formation of multimers/complexes, and variations in oxidation.

At the other extreme in terms of complexity, with both of the 505(b)(2) approvals of recombinant and natural forms of hyaluronidase FDA considered hyaluronidase to be a complex uncharacterizable natural product, with this allowing FDA to consider different products with comparable activity to be comparable/similar.

What is a Biopharmaceutical?

The multitude of definitions as to what constitutes a biopharmaceutical can make it difficult to compare approvals reported by different sources. For clarity, we define biopharmaceutical as pharmaceuticals inherently biological in nature due to their method of manufacture; specifically those using biotechnology and involving the use of live organisms. This is by far the definition preferred by those in the biopharmaceutical industry, according to a recent survey.

This definition does not include small molecule and other drugs inherently chemical, not biological; does not include drugs just because biotechnology-like companies are involved; and does not simply consider or redefine all or selected modern pharmaceuticals to be biopharmaceuticals.

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FDA Biopharmaceuticals Approvals, January 1, 2005–July 1, 2006

Names	Company	Date	Type	Indication
VEGF Mab Fab, rDNA—Lucentis*	Genentech	6/30/2006	BLA	Age-related macular degeneration
Somatropin, rDNA/Sandoz—Omnitrope* somatotropin; human growth hormone	Sandoz (sub. of Novartis)	5/30/2006	NDA	Growth hormone deficiency; short stature
HPV vaccine, rDNA/Merck—Gardasil* ; human papillomavirus (HPV) virus-like proteins (VLPs)	Merck & Co.	6/8/2006	BLA	Vaccine against cervical cancer due to HPV infection
Varicella Virus Vaccine/adult—Zostavax* varicella virus vaccine	Merck & Co.	5/25/2006	BLA	Adult vaccine against herpes zoster or shingles
Glucosidase, rDNA—Myozyme*	Genzyme	4/28/2006	NDA	Pompe disease
Rotavirus Vaccine, rDNA/Merck—RotaTeq*	Merck & Co.	2/3/2006	NDA	Infant vaccine against rotavirus
Insulin, rDNA, inhaled/Pfizer—Exubera*	Pfizer	1/27/2006	NDA	Pompe disease
Hepatitis B Immune Globulin, i.m./Cangene—HepaGam B*	Genzyme	4/28/2006	BLA	Hepatitis B virus infection
CTLA4-Ig, rDNA—Orencia* ; cytotoxic T-lymphocyte-associated antigen 4-Immunoglobulin G1 fragment fusion protein	Bristol-Myers Squibb	12/26/2005	BLA	Rheumatoid arthritis
Insulin-like Growth Factor-1/IGFBP-3, rDNA—IPLEX* ; Insulin-like growth factor I--insulin-like growth factor-binding-3 protein complex	Insmed	12/12/2005	NDA	Growth failure, pediatric
Hyaluronidase, rDNA—Hyalenex* ; Enhanze SC; hyaluronidase, recombinant human	Halozyme Therapeutics; marketing by Baxter	12/5/2005	NDA	Spreading agent (local anesthesia, contrast agents, and subcutaneous fluid replacement)
Hyaluronidase, ovine/Primapharm—Hydase*	PrimaPharm	10/25/2005	NDA	Spreading agent (local anesthesia, contrast agents and subcutaneous fluid replacement)
PDGF, rDNA/Bone matrix—GEM 21S* ; platelet-derived growth factor-BB, with inorganic bone matrix	BioMimetic Therapeutics; marketing by Osteohealth (Luitpold/ Sankyo)	10/21/2005	PMA	Periodontal bone defects and associated gingival recession
Measles Mumps Rubella & Varicella Vaccine—ProQuad*	Merck & Co.	9/6/2005	BLA	Pediatric vaccine against measles, mumps, German measles and chickenpox
Influenza Vaccine/GSK—Fluarix*	GlaxoSmithKline	8/31/2005	BLA	Vaccination against influenza
Insulin-like Growth Factor-1, rDNA/Tercica—Increlex* ; IGF-1	Tercica (with Genentech)	8/31/2005	NDA	Growth failure, pediatric
Calcitonin, rDNA—Fortical*	Unigene; marketed by Upsher-Smith	8/15/2005	NDA	Postmenopausal osteoporosis
Insulin detemir, rDNA—Levemir*	Novo Nordisk	6/17/2005	NDA	Diabetes mellitus (types 1 and 2)
dTpa booster/Sanofi—Adacel* ; Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Adsorbed; dTpa	Sanofi Pasteur	6/10/2005	BLA	Booster vaccine against tetanus, diphtheria, and pertussis (whooping cough)
Arylsulfatase B, rDNA—Naglazyme* ; N-acetyl-galactosamine 4-sulfatase; chondroitinase	BioMarin Pharma	5/31/2005	NDA	Mucopolysaccharidosis VI
dTpa booster/GSK—Boostrix* ; Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Adsorbed; dTpa	GlaxoSmithKline	5/3/2005	BLA	Booster vaccine against tetanus, diphtheria, and pertussis (whooping cough)
Tetanus Toxoid, conc.—Tetanus Toxoid Concentrate (For Further Manufacturing Use)	Chiron/Novartis	5/3/2005	BLA	Component of Boostrix (see above entry)
Vaccinia Immune Globulin—VIG; VIGIV	Cangene	5/2/2005	BLA	Treats complications from smallpox vaccination
Immune Globulin (IGIV)/Baxter—Gammagard Liquid* ; IGIV	Baxter	4/27/2005	BLA	Primary immune deficiency
Hyaluronidase, rDNA—Cumulase* ; rHuPH20	Halozyme Therapeutics	4/19/2005	510(k)	In vitro fertilization (IVF)
Vaccinia Immune Globulin—VIG; VIVIG	DynPort Vaccine	2/18/2005	BLA	Treats complications from smallpox vaccination
Thrombin, conc.—Thrombin (Human) (For Further Manufacturing Use)	Baxter	2/18/2005	BLA	Use in FloSeal fibrin sealant (to control bleeding)
Meningococcal Conjugates Vaccine—Menactra* ; Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine	Sanofi Pasteur	1/14/2005	BLA	Vaccination against bacterial meningitis

This table presents names, followed by U.S. trademark marked names*, company, U.S. marketing company; approval date: type (BLA for biologics; NDA for drugs; and PMA or 510(k) for medical devices); rDNA indicates whether product is a recombinant protein or not.