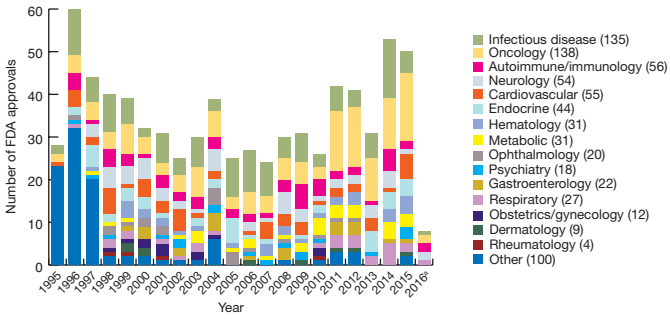
Drug pipeline: 2Q16

Laura DeFrancesco

The US Food and Drug Administration experienced another slow quarter, but among the approved drugs are three accelerated approvals and a biosimilar approval. The European Medicines Agency gave the green light to Strimvelis, a hematopoietic-stem-cell-mediated gene therapy for a severe combined immunodeficiency indication; two other gene therapies showed efficacy in human testing. Regulatory decisions for several innovative drugs are coming up.

Historic US regulatory approvals by lead indication



[a]2015 partial year from January 1 to June 30. Numbers in parentheses after legend are total approvals since 1995.

Notable clinical trial results (2Q16)

Drug/company	Indication	Summary
Ixmyelocel-T/ Vericel	Congestive heart failure	4/4/2016. Phase 2b trial of autologous bone-marrow-derived, *in-vitro*-expanded mixture of $CD90^+$ mesenchymal stromal cells, $CD14^+$ macrophages and $CD45^+$ cells reduced cardiovascular events by 37% in 126 heart patients, but had no effect on heart structure. *Lancet* **387**, 2412–2421 (2016)
AAV.REP1/ NightStaRx	Choroideremia	4/27/2019. Phase 1/2 trial of adeno-associated virus subtype 2 (AAV2) gene therapy supplying *CHM* gene resulted in improvement in 2/6 patients at 3.5 years. *N. Engl. J. Med.* **374**, 1996–1998 (2016)
GSK-2696274/ GlaxoSmithKline	Metachromatic leukodystrophy	6/8/2016. Phase 1/2 trial of lentiviral gene therapy supplying arylsulfatase A cDNA halted progression or stopped onset in 8/9 children. *Lancet* doi:10.1016/S0140-6736(16)30374-9 (8 June 2016)
Inotuzumab ozogamicin/Pfizer	Acute lymphocytic leukemia	6/13/2016. Phase 3 trial of anti-CD22 humanized IgG4 mAb covalently conjugated via an acetyl butyrate linker to N-acetyl-gamma-calecheamicin dimethyl hydrazide resulted in 80% complete response versus 30% with range of chemotherapies. *N. Engl. J. Med.* doi: 10.1056/NEJMoa1509277 (12 June 2016)
Olaratumab/ Eli Lilly	Sarcoma	6/9/2016. Phase 2 trial of human IgG1 mAb against platelet derived growth factor receptor alpha (PDGFRα) with doxorubicin gave 11 month improvement in survival over doxorubicin alone. *Lancet* doi:10.1016/S0140-6736(16)30587-6 (9 June 2016)

mAb, monoclonal antibody. Source: BioMedTracker, a service of Sagient Research (http://www.biomedtracker.com)

Notable regulatory setbacks (2Q16)

Drug/company	Indication	Drug information
ZS-9 (sodium zirconium cyclosilicat)/ AstraZeneca	Hyperkalemia	5/27/2016. FDA issued a complete response letter for this small-molecule potassium ion trap due to manufacturing issues
Zumagev (zastumotide)/ GlaxoSmithKline	Non-small cell lung cancer	4/2/2014. Company suspended phase 3 trial of MAGE-A3 antigen in combination with adjuvant (QS-21/monophosphoryl lipid A/agatolimod) owing to inability to identify gene signature for patients that would benefit
PNT2258/ProNAi	Diffuse large B-cell lymphoma/solid tumors	6/6/2016. Company suspended development of 24 base single-stranded phosphodiester DNA oligodeoxynucleotide encapsulated in a α-(3′-O-cholesteryloxycarbonyl)-δ-(N-ethylmorpholine)-succinamide protective amphoteric liposome (Smarticle) due to modest efficacy at interim analysis
CAT-2054/Catabasis	Dyslipidemia/ hypercholesterolemia	6/7/2016. Company suspended phase 2a trial of conjugate of eicosapentaenoic acid and vitamin B3 via an amide/ester bond linker (SMART) technology because primary endpoint of reduced LDL cholesterol was not met

FDA, US Food and Drug Administration. Source: BioMedTracker, a service of Sagient Research (http://www.biomedtracker.com)

Notable regulatory approvals (2Q16)

Drug/company	Indication	Drug information
Inflectra (infliximab-dyyb)/Celltrion	RA, ankylosing spondylitis, CD, psoriasis, PA, UC	4/4/2016. FDA approved a biosimilar for Janssen's Remicade, a chimeric IgG1kappa mAb against tumor necrosis factor alpha
Venclexta (venetoclax)/ AbbVie	17p-deleted chronic lymphocytic leukemia	4/11/2016. FDA granted accelerated approval for this small molecule BH3 mimetic acting as selective Bcl-2 inhibitor
Tecentriq (atezolizumab)/Roche	Bladder cancer	5/18/2016. FDA granted accelerated approval for this human IgG1 anti-PD1 mAb with an engineered Fc domain that eliminates antibody-dependent cellular cytotoxicity
Ocaliva (obeticholic acid)/Intercept	Primary biliary cirrhosis, hepatic fibrosis	5/27/2016. FDA granted accelerated approval for this farnesoid X receptor (FXR) agonist
Afstyla (factor VIII-single chain)/CSL	Hemophilia A	5/26/2016. FDA approved this recombinant human single-chain B-domain truncated factor VIII with longer half-life
Epclusa (sofosbuvir, velpastasvir)/ Gilead	Hepatitis C	6/28/2016. FDA approved pan-genotype single pill combination of nucleotide analog NS5B polymerase inhibitor and NS5A protein inhibitor
Galafold (migalastat)/ GlaxoSmithKline	Fabry's disease	5/26/2016. EMA approved 1-deoxygalactonojirimycin chaperone that stabilizes mutated alpha-galactosidase A
Strimvelis (GSK2696273)/ GlaxoSmithKline	Severe combined immunodeficiency	5/26/2016. EMA approved autologous $CD34^+$ human hematopoietic stem cells modified with Moloney murine virus with human gene for adenosine deaminase
Biosimilar Infliximab/ Samsung Bioepis	RA, ankylosing spondylitis, CD, psoriasis, PA, UC	5/30/2016. EMA approved biosimilar for Janssen's Remicade
Breakthrough drug		
PVS-RIPO/Duke University Medical Center	Malignant glioma; anaplastic astrocytoma and glioblastoma	5/16/2016. FDA granted breakthrough drug status to live attenuated recombinant serotype 1 poliovirus vaccine containing a heterologous internal ribosomal entry site from human rhinovirus type 2

mAb, monoclonal antibody; FDA, US Food and Drug Administration; EMA, European Medicines Agency; RA, rheumatoid arthritis; CD, Crohn's disease; PA, psoriatic arthritis; UC, ulcerative colitis. Source: BioMedTracker, a service of Sagient Research (http://www.biomedtracker.com)

Notable upcoming regulatory decisions (3Q16)

Drug/company	Indication	Summary
Biosimilar pegfilgrastim/Apotex	Neutropenia/leukopenia	7/15/2016. FDA PDUFA date for biosimilar for Amgen's Neulasta (recombinant human granulocyte colony-stimulating factor)
Bezlotoxumab/Merck	*Clostridium difficile*-associated diarrhea/infection	7/22/2016. FDA PDUFA date for human IgG1 mAb against *C. difficile* enterotoxin B
Lifitegrast (SAR1118)/Shire	Dry eye	7/22/2016. FDA PDUFA date for small-molecule tetrahydroisoquinoline-derived integrin antagonist that blocks lymphocyte function-associated antigen-1/intercellular adhesion molecule 1
Lyxumia (lixisenatide)/Sanofi	Diabetes mellitus, type II	7/29/2016. FDA PDUFA date for 44-amino-acid analog of exendin 4 (glucagon-like peptide 1 mimic) modified at the C-terminal with the removal of a proline residue and addition of six lysine residues
Eteplirsen/Sarepta	Muscular dystrophy	7/31/2016. FDA PDUFA data for phosphorodiamidate morpholino oligomer that promotes skipping of exon 51 of dystrophin gene
Graspa (ERY-ASP)/ ERYTECH Pharma	Acute lymphoblastic leukemia	8/1/2016. EMA decision on human L-asparaginase loaded into erythrocytes by osmotic stress
Biosimilar pegfilgrastim/Sandoz	Neutropenia/leukopenia	8/4/2016. FDA PDUFA date for biosimilar for Amgen's Neulasta
Biosimilar Etanercept/Sandoz	RA, ankylosing spondylitis, psoriasis, PA, UC	8/15/2016. FDA PDUFA date for biosimilar of Amgen's Enbrel (fusion of Fc portion of IgG with tumor necrosis factor alpha receptor)
Andexxa (andexanet alfa)/Portola	Factor Xa toxicity	8/17/2016. FDA PDUFA date for this antidote, a truncated recombinant human factor Xa lacking a membrane-binding γ-carboxyglutamic acid domain and containing a S419A mutation in the protease site and RKRRKR in place of the C-terminal factor X-activation peptide
Etelcalcetide/Amgen	Hyperparathyroidism	8/24/2016. FDA PDUFA date for first long-acting isozyme-selective peptide, comprising a linear chain of seven D-amino acids, with a D-cysteine linked to an L-cysteine via a disulfide bond, that inhibits protein kinase C epsilon and agonist of the calcium-sensing receptor
Zalmoxis (TK)/ MolMed	Bone marrow/stem cell transplant	8/29/2016. EMA decision on donor lymphocytes transfected with herpes simplex virus thymidine kinase gene to prevent graft-versus-host disease in partially compatible donors

FDA, US Food and Drug Administration; PDUFA, Prescription Drug User Fee Act; mAb, monoclonal antibody; RA, rheumatoid arthritis; CD, Crohn's disease; PA, psoriatic arthritis; UC, ulcerative colitis. Source: BioMedTracker, a service of Sagient Research (http://www.biomedtracker.com/)

Laura DeFrancesco is Senior Editor at Nature Biotechnology.