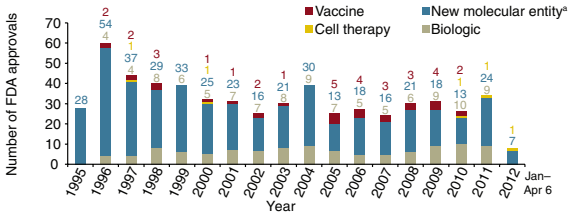
Drug pipeline: 1Q12

Craig Mak

The rate of US Food and Drug Administration (FDA) approvals has been slower than for the same time last year. Notable registrations include small molecules Erivedge, a first-in-class Smoothened inhibitor for basal-cell carcinoma, and Kalydeco, a potentiator of G551D-mutated cystic fibrosis transmembrane conductance regulator for cystic fibrosis. The curse of neurodegenerative disorders again claimed two experimental drugs: Medivation's Dimebon and Trophos' Olesoxime. Shire ditched its US marketing application for Replagal, a human glucocerebrosidase available in Europe since 2001, after the FDA required further efficacy trials.



[a]The new molecular entity (NME) class includes mainly small-molecule drugs, but also steroid, synthetic peptide, and mixed compounds.
Source: U.S. Food and Drug Administration (FDA), excluding non-NME drugs and new formulations of existing drugs.

Notable regulatory approvals (Q1 2012)

Drug/company	Indication	Drug information
Voraxaze (glucarpidase)/BTG	Drug toxicity	1/17/2012, FDA. Recombinant bacterial enzyme that rapidly hydrolyzes methotrexate.
Bydureon (exenatide)/Amylin	Type 2 diabetes	01/27/2012, FDA. Synthetic exendin-4 in a matrix of poly-(DL-lactide-co-glycolide).
Picato (ingenol mebutate)/Leo Pharma	Actinic keratoses	1/23/2012, FDA. Cytotoxic topical gel derived from *Euphorbia peplus* sap that activates protein kinase C.
Erivedge (vismodegib)/Genentech	Basal-cell carcinoma	1/30/2012, FDA. Small-molecule antagonist of Smoothened.
Kalydeco (ivacaftor)/Vertex	Cystic fibrosis	1/31/2012, FDA. Small-molecule potentiator of G551D-mutated cystic fibrosis transmembrane conductance regulator.
Vepacel/Baxter	Influenza	2/17/2012, EMA. Vero cell culture–produced prepandemic vaccine against H5N1 subtype of influenza A.
Surfaxin (lucinactant)/Discovery Laboratories	Respiratory distress syndrome	3/6/2012, FDA. Synthetic surfactant containing 21-amino-acid peptide sinapultide (KL4) mimic of human surfactant protein B.
Omontys (peginesatide)/Affymax	Anemia due to chronic renal failure	3/27/2012, FDA. PEGylated synthetic linked dipeptide erythropoiesis-stimulating agent.

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

Notable trial results (Q1 2012)

Drug/company	Indication	Result summary
Vorapaxar/Merck	Cardiovascular disease	Phase 3 trial showed that the small-molecule thrombin-receptor antagonist reduced by 12% the collective risk of cardiovascular death, heart attack, stroke or urgent coronary revascularization compared with placebo plus standard of care (*N. Engl. J. Med.* published online, doi:10.1056/NEJMoa1200933 (12 April 2012)).
Ampligen (rintatolimod)/Hemispherx Biopharma	Chronic fatigue syndrome	Phase 3 trial showed that the double-stranded RNA (polyinosic:polycytidylic acid with uridine at every ~13th nucleoside) improved intrapatient placebo-adjusted exercise tolerance by 21.3% (*PLoS One* published online, doi:10.1371/journal.pone.0031334 (14 March 2012)).
Heplisav/Dynavax Technologies	Hepatitis B	Phase 3 trial of the toll-like receptor 9 agonist cytosine–phosphate–guanine phosphorothioate paired with hepatitis B surface antigen (HBsAg) demonstrated superior/earlier seroprotection compared to HBsAg alone (*Vaccine* published online, doi:10.1016/j.vaccine.2012.02.001 (14 February 2012); 10.1016/j.vaccine.2012.01.087 (8 February 2012)).
MK-7243/Merck	Allergy	Phase 3 trial showed that this allergen extract of timothy grass pollen reduced rhinoconjunctivitis daily symptom score (*J. Allergy Clin. Immunol.* published online, doi:10.1016/j.jaci.2011.12.973 (29 January 2012)).
Zevalin (ibritumomab tiuxetan)/Spectrum Pharmaceuticals	Non-Hodgkin's lymphoma (NHL)	Phase 3 trial showed the anti-CD20 mouse monoclonal antibody (mAb) conjugated to radioisotope to be as effective as chemotherapy-conditioning regimen for autologous stem-cell transplantation (*Cancer* published online, doi:10.1002/cncr.27418 (17 January 2012)).
Ixekizumab/Eli Lilly & Company	Psoriasis	Phase 2 trial showed that the humanized mAb against IL-17 reduced psoriasis area-and-severity index (PASI) score by >75% at week 12 (*N. Engl. J. Med.* **366**, 1190–1199, 2012).
Brodalumab/Amgen	Psoriasis	Phase 2 trial of the human mAb targeting IL-17 receptor demonstrated improvement in PASI score from baseline at week 12 (*N. Engl. J. Med.* **366**, 1181–1189, 2012).

Notable trial results (Q1 2012) (continued)

AMG 386/Amgen	Ovarian cancer	Phase 2 trial demonstrated that the Fc region of human IgG1 fused to anti-angiopoietin 1/2 synthetic peptide had tolerable toxicity profile in combination with paclitaxel (*J. Clin. Oncol.* **30**, 362–371, 2011).
Elobixibat/Albireo Pharma	Chronic idiopathic constipation	Phase 2 trial of the small-molecule inhibitor of ileal bile acid transporter showed that it accelerated colonic transit and loosened stool consistency in female patients (*Am. J. Gastroenterol.* published online, doi:10.1038/ajg.2011.285 (30 August 2011)).
Tosedostat/Cell Therapeutics	Acute myelogenous leukemia (AML)	Phase 2b trial of the small-molecule aminopeptidase/leukotriene A4 hydrolase inhibitor demonstrated its efficacy and favorable toxicity profile in elderly patients with relapsed/refractory AML.

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

Notable upcoming regulatory decisions (Q2–Q3 2011)

Drug/company	Indication	Expected regulatory decision
Pasireotide/Novartis	Cushing's syndrome	EU approval decision[a]. Pasireotide is a cyclohexapeptide somatostatin analog that broadly agonizes all somatostatin receptor subtypes.
Uplyso (taliglucerase alfa)/Pfizer	Gaucher's disease	PDUFA[a]. Uplyso is a plant cell–expressed recombinant form of human glucocerebrosidase.
Glybera (alipogene tiparvovec)/Amsterdam Molecular Therapeutics	Lipoprotein lipase deficiency	5/1/12–5/31/12 EU standing committee final decision. Glybera is a recombinant adeno-associated viral vector expressing Ser447X variant of human lipoprotein lipase gene.
Pertuzumab/Roche	Breast cancer	6/8/12 PDUFA. Pertuzamab is an anti-HER2 humanized mAb.
Lorqess (lorcaserin hydrochloride)/Arena Pharmaceuticals	Obesity	6/27/12 PDUFA. Lorqess is a selective small-molecule agonist of 5-hydroxytryptamine 2C receptors.
FluBlok/Protein Sciences	Influenza	Now–6/30/12 PDUFA. FluBlok is a seasonal trivalent influenza vaccine manufactured using baculovirus in modified Sf9 insect cells.
Degludec/Novo Nordisk	Diabetes mellitus	7/27/12 PDUFA. Degludec is a long-acting insulin analog containing a ThrB30 deletion and 16-carbon fatty di-acid attached to LysB29 via a glutamic acid spacer.
Carfilzomib/Onyx Pharmaceuticals	Multiple myeloma	7/27/12 PDUFA. Carfilzomib is a tetrapeptide epoxyketone proteasome inhibitor (epoxomicin derivative).
Gattex (teduglutide)/NPS Pharmaceuticals	Short bowel syndrome	9/28/2012 PDUFA. Gattex is a synthetic analog of glucagon-like peptide-2 with an N-terminal Ala2Gly substitution.
Qnexa (phentermine and topiramate)/Vivus	Obesity	07/17/2012 PDUFA. Qnexa is a combination of the small molecules phentermine and topiramate.

[a]Decision expected as *Nature Biotechnology* went to press.
Source: BioMedTracker, a service of Sagient Research (http://www.biomedtracker.com/). PDUFA, Prescription Drug User Fee Act.

Notable regulatory setbacks (Q1 2012)

Drug/company	Indication	Setback summary
Olesoxime/Trophos	Amyotrophic lateral sclerosis	12/12/11. Phase 3 trial of cholest-4-en-3-one oxime targeting two components of the mitochondrial permeability transition pore did not meet primary endpoint.
Dimebon (latrepirdine)/Medivation & Pfizer	Alzheimer's disease	1/16/12. Development of small-molecule antihistamine was discontinued after failure to meet primary endpoints.
Saridegib/Infinity Pharmaceuticals	Pancreatic cancer	1/27/12. Phase 1b/2 trial stopped after IPI-926, a derivative of natural product cyclopamine that antagonizes ligand-dependent Smoothened signaling, showed lower survival in placebo arm.
Diamyd/Diamyd Medical	Diabetes mellitus, type 1	2/2/12. Phase 3 trial of recombinant human glutamic acid decarboxylase protein did not meet primary endpoint of preserving beta cell function (*N. Engl. J. Med.* **366**, 433–442, 2012.)
Ulimorelin/Tranzyme Pharma	Postoperative ileus	3/12/12. NDA filing of ghrelin receptor agonist suspended after phase 3 trial failed to meet primary and secondary endpoints.
Replagal (agalsidase alfa)/Shire Pharmaceuticals	Fabry's disease	3/14/12. Company withdrew BLA after interactions with the FDA suggested that the agency will require additional controlled trials for approval.

Source: BioMedTracker, a service of Sagient Research (http://www.biomedtracker.com/). BLA, biologic license application; FDA, Food and Drug Administration (USA); NDA, new drug application.

Craig Mak is Associate Editor, Nature Biotechnology.