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2009 FDA drug approvals

In a year in which regulators and drug companies gained familiarity with risk management strategies, the number of new drug approvals was similar to that in 2008.

In 2009, 19 new molecular entities (NMEs) and 6 biologic licence applications (BLAs) were approved by the FDA's Center for Drug Evaluation and Research (CDER) — 1 more than in 2008 (FIG. 1; TABLES 1,2).

"While it is encouraging that numbers are nudging in the right direction, the volume of approvals is still much lower than the industry and investors would like it to be," says Andrew Jones, senior pharmaceutical industry analyst, Ernst & Young, London, UK. "It will require a few more years, and more significant increases in approvals, before it becomes more appropriate to talk about R&D productivity recovery."

To assess productivity, it is also important to consider the novel products approved by the Center for Biologics Evaluation and Research (CBER), continues Jones. (CBER evaluates allergenics, blood and blood products, cellular and gene therapy products, tissue and tissue products, vaccines and xenotransplantation.) Christopher Milne, Associate Director, Tufts Center for the Study of Drug Development, Tufts University, Boston, Massachusetts, USA, agrees with Jones, noting that adding novel CBER approvals brings the total of new drugs and biologics to ~35 in 2009. However, he includes the caveat that what is considered 'important' in terms of the CBER approvals "is in the eye of the beholder." Nevertheless, "some may represent important breakthroughs for patients or big revenues for industry — particularly when you include vaccines and other recombinant products that might not be approved by CDER," says Jones.

2009 approval highlights

One such product that was approved by CBER, but not CDER, was recombinant human antithrombin (ATryn; GTC Biotherapeutics) for the treatment of hereditary antithrombin deficiency. "From a technology perspective, ATryn is interesting because it is the first therapeutic protein to be derived from a transgenic animal [a goat]," says Jones. "And vaccines like Cervarix [a prophylactic vaccine against human papilloma virus types 16 and 18 developed by GlaxoSmithKline, which was approved by CBER in October 2009] have the potential to add significant value to the health-care system, as well as to shareholders," he says.

"In terms of novelty, I would mention Johnson & Johnson's Stelara [ustekinumab] because it is first in class, targeting interleukin-12 and -23," says Jones. He also highlights Allos Therapeutics's NME pralatrexate (Folotyn) as the first drug to be approved for relapsed or refractory peripheral T cell lymphoma.

From a commercial perspective, Michael Hay, senior analyst at BioMedTracker, Sagient Research Systems, San Diego, USA, highlights saxagliptin (Onglyza; Bristol–Myers Squibb/AstraZeneca), which is the second dipeptidyl peptidase 4 (DPP4) inhibitor to be approved by the FDA for the treatment of type 2 diabetes. "The first DPP4 inhibitor Januvia [sitagliptin] is a big drug, and we expect Onglyza to be over a billion dollar drug as well."

> "Although the FDA has corrected much of their staffing problem, they are still underfunded and overworked."

Another approval Hay considers to be important is ecallantide (Kalbitor; Dyax Corporation) for the treatment of hereditary angioedema (HAE). "There weren't any treatments available for HAE in the US until Cinryze [a serum-derived C1 esterase inhibitor purified from blood plasma that is delivered intravenously] was approved in 2008," he says. "But now patients have an alternative treatment option for this rare disorder and, in addition, Kalbitor is administered subcutaneously," he explains.

Big pharma's presence

The substantial presence of specialty pharmaceuticals companies in the CDER approval list, as well as the limited presence of several large pharmaceutical companies, is notable, say Jones. "We know that there remains a productivity shortfall and big pharma still faces challenges. However, bucking that trend is Novartis, which had three approvals — Afinitor [everolimus, for the treatment of renal cell carcinoma], Coartem [artemether and lumefantrine, for the treatment of malaria] and Ilaris [canakinumab, for the treatment of cryopyrin-associated periodic syndromes]. You could argue that GlaxoSmithKline also had a particularly good year if you include vaccines, with the

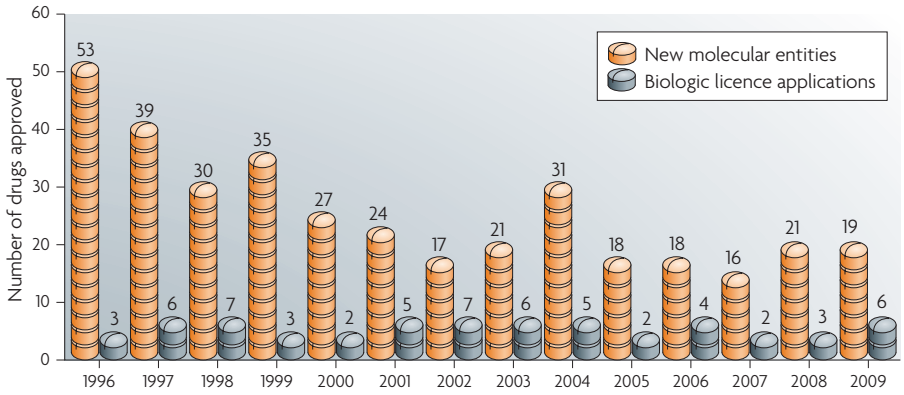

Figure 1 | **FDA drug approvals.** New molecular entities and biologic licence applications approved by the US FDA's Center for Drug Evaluation and Research by year.

approval of Cervarix and Hiberix [a prophylactic vaccine against *Haemophilus influenzae* type b infection], in addition to Arzerra [ofatumumab, for the treatment of chronic lymphocytic leukaemia, developed in partnership with Genmab] and Votrient [pazopanib, for the treatment of renal cell carcinoma]."

Biotechnology companies contributed four of the CDER approvals — pralatrexate, ofatumumab, romidepsin (Istodax; Gloucester Pharmaceuticals) and ecallantide — and two BLAs that were granted by the CBER: for antithrombin and ferumoxytol (Feraheme; AMAG Pharmaceuticals). "Six approvals from our industry is a fairly low number," says Eric Schmidt, Biotechnology Equity Research Analyst, Cowen and Company, New York, USA. "In recent years we have had closer to 10, if not 15, new drug approvals, so 6 is a disappointing output." He adds, "But there isn't a trend here, such as the biotechnology industry becoming less productive. It is hard to judge the industry based on a single calendar year that starts and ends at an arbitrary point in time."

Nevertheless, the percentage of total approvals for the year that were for new biologics (24%) was higher than for any previous years, notes Jones. "We expect BLAs to continue to rise in coming years, as a reflection on the investment being made by big pharma into biopharmaceuticals. In fact, four of the six biologics approved in 2009 were submitted by big pharmaceutical companies," he says.

Therapeutic areas and priority review

Over half of the CDER approvals (15 out of 25) were in four therapeutic areas: autoimmune diseases (three approvals), cancer (five approvals), cardiovascular indications (three approvals) and neurological disorders (four approvals). Seven of the nine agents given priority reviews in 2009 also fell into one of these four areas. "These products are considered an advance over what is currently on the market, but their rate of approval is somewhat flat — the same as in 2007 and 2008," comments Milne. However, he adds, "there was a good representation of new drugs for rare disorders." Of the nine priority reviews, six had also received orphan drug designation from the FDA (TABLES 1,2).

Given the ongoing challenge presented by antibiotic-resistant bacteria, Milne considers that the approval of two new antimicrobials — besifloxacin (Besivance; Bausch and Lomb) and telavancin (Vibativ; Theravance/Astellas) — is important, although more are needed. He also highlights diabetes as another area in which more approvals would be particularly desirable. "There was just one diabetes drug approved, but the impact of the disease is huge."

Table 1 | **New biologics approved by the US FDA's Center for Drug Evaluation and Research in 2009***

Generic name (Trade name)	Company‡	Indication (URL of label information)	Properties	Date
Golimumab (Simponi)	Centocor Ortho Biotech (a subsidiary of J&J)	Rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis (http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/125289s006lbl.pdf)	Human mAb specific for tumour necrosis factor	24 Apr (S)
Abobotulinum-toxin A (Dysport)	Ipsen	Cervical dystonia and glabellar lines (http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/125274s0000s0001lbl.pdf)	Acetylcholine release inhibitor and neuromuscular blocking agent	29 Apr (S)
Canakinumab (Ilaris)	Novartis	Cryopyrin-associated periodic syndromes (http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/125319s000lbl.pdf)	Human mAb specific for interleukin-1β	17 Jun (P,O)
Ustekinumab (Stelara)	Centocor Ortho Biotech (a subsidiary of J&J)	Moderate-to-severe plaque psoriasis (http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/125261lbl.pdf)	Human mAb specific for the p40 subunit of interleukin-12 and -23	25 Sep (S)
Ofatumumab (Arzerra)	GlaxoSmithKline (developed with Genmab)	Chronic lymphocytic leukaemia (http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/125326lbl.pdf)	Human mAb specific for CD20	26 Oct (P,O)
Ecallantide (Kalbitor)	Dyax Corporation	Hereditary angioedema (http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/125277lbl.pdf)	Plasma kallikrein inhibitor	27 Nov (P,O)

J&J, Johnson & Johnson; mAb, monoclonal antibody; O, FDA orphan designation; P, FDA priority review; S, FDA standard review. *CDER also approved a biologic licence application for a branded version of interferon-β1b (Extavia; Novartis). This agent has not been included in the table because interferon-β1b products have been marketed in the United States prior to 2009. ‡The company that submitted the original biologic licence application to the FDA.

Table 2 | **New molecular entities approved by the US FDA's Center for Drug Evaluation and Research in 2009**

Generic name (Trade name)	Company*	Indication (URL of label information)	Properties	Date
Milnacipran HCl (Savella)	Cypress Bioscience	Fibromyalgia (http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/022256s001lbl.pdf)	Selective serotonin and noradrenaline reuptake inhibitor	14 Jan (S)
Febuxostat (Uloric)	Takeda	Hyperuricaemia in patients with gout (http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/021856lbl.pdf)	Xanthine oxidase inhibitor	13 Feb (S)
Everolimus (Afinitor)	Novartis	Renal cell carcinoma (http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/022334lbl.pdf)	Mammalian target of rapamycin inhibitor	30 Mar (P)
Artemether–lumefantrine (Coartem)	Novartis	Malaria (http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/022268lbl.pdf)	Unspecified antiparasitic drug target	7 Apr (P,O)
Benzyl alcohol (Ulesfia)	Sciele Pharma (now known as Shionogi Pharma)	Head lice (http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/022129lbl.pdf)	Topical pediculocide	9 Apr (S)
Iloperidone (Fanapt)	Vanda Pharmaceuticals	Schizophrenia (http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/022192lbl.pdf)	Atypical antipsychotic agent, thought to act through antagonist activity at the dopamine type 2 and serotonin type 2 receptors	6 May (S)
Tolvaptan (Samsca)	Otsuka	Hypervolaemic and euvolaemic hyponatraemia, including patients with heart failure, cirrhosis and syndrome of inappropriate antidiuretic hormone (http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/022275lbl.pdf)	Selective vasopressin V_2 receptor antagonist	19 May (S)
Besifloxacin (Besivance)	Bausch and Lomb	Bacterial conjunctivitis (http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/022308lbl.pdf)	Fluoroquinolone antimicrobial agent	28 May (S)

Indeed, an approval decision for another potential diabetes drug, the long-acting glucagon-like peptide 1 (GLP1) analogue liraglutide, was delayed in 2009. At the end of 2009, the developer Novo Nordisk announced that formal feedback on the regulatory decision about liraglutide was expected from the FDA within weeks, but this had not been received at the time of going to press.

A factor that has delayed the regulatory decision on liraglutide is the potential significance of an increased incidence of medullary thyroid cancer that has been observed in preclinical studies. "The effect was observed in rodents, and the FDA is worried that it might affect humans. It will be interesting to see how the FDA will address this potential problem," says Hay. "If they find it to be a class effect, it could derail development of all the GLP1 drugs, or they might approve them with a warning, or they could find that certain drugs have a higher degree of risk [than other drugs in the class]."

It is thought that the FDA is probably using the preclinical data for a supplementary new drug application (NDA) that it is also currently reviewing, for exenatide LAR (developed by Amylin/Lilly/Alkermes) — a once-weekly formulation of the approved subcutaneous GLP1 agonist exenatide (Byetta; Amylin/Lilly) — to determine whether the observations for liraglutide are a class effect (*Nature Rev. Drug Discov.* **9**, 11; 2010).

Apart from liraglutide and exenatide LAR, another eagerly awaited diabetes therapy is Mannkind's fast-acting inhaled insulin, Afrezza. The Prescription Drug User Fee Act (PDUFA) date for Afrezza was 16 January 2010, but this was delayed because the FDA had not finished inspecting the manufacturing plant that makes the insulin.

> "We are starting to see some of the regulatory 'squeeze' easing."

Industry observers are interested in Afrezza because Pfizer's inhaled insulin, Exubera, was withdrawn in October 2007 owing to failure in the market (*Nature Rev. Drug Discov.* **7**, 189–190; 2008). "We are waiting to see if Mannkind can achieve what big pharma was not able to do with inhaled insulin," says Jones. One of the reasons why Exubera failed is because patients were required to have lung function tests, says Hay. "Also, with Exubera there appeared to be an increased risk of lung cancer. Mannkind think that they will not have to do lung function tests as Afrezza looks safer, and any cancer cases they have seen have been unrelated to the drug. So, it will be interesting to see what decision the FDA makes in regard to both the approval and the label," adds Hay.

Regulatory evolution

The delay to Mannkind's PDUFA date for Afrezza will come as no surprise to industry observers as delays in general continue to be a feature of the regulatory process. "Although the FDA has corrected much of their staffing problem, they are still underfunded and overworked," says Schmidt. There is also a general agreement that, although staffing levels at the FDA have been addressed, there will be a lag time in which the new reviewers are trained before the performance goal of meeting 90% of the priority and standard review times will be achieved. Currently, 69% of priority review deadlines and 83% of standard review deadlines are met.

The most common reason for regulatory delays is the requirement for risk evaluation and mitigation strategies (REMS), which were introduced in 2008. "Kalbitor was put back in March, for example," notes Jones, when Dyax received a complete response letter from the FDA requesting REMS. Dyax responded

Table 2 (cont.) | **New molecular entities approved by the US FDA's Center for Drug Evaluation and Research in 2009**

Generic name (Trade name)	Company*	Indication (URL of label information)	Properties	Date
Dronedarone HCl (Multaq)	Sanofi–Aventis	Atrial fibrillation and atrial flutter (http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/022425lbl.pdf)	Mechanism of action unknown, but dronedarone has an anti-arrhythmic effect	1 Jul (P)
Prasugrel (Effient)	Lilly (developed with Daiichi Sankyo)	Reduction of thrombotic cardiovascular events in patients with acute coronary syndrome undergoing percutaneous coronary intervention (http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/022307s000lbl.pdf)	Platelet $P2Y_{12}$ purinoceptor inhibitor	10 Jul (P)
Saxagliptin (Onglyza)	Bristol–Myers Squibb (developed with AstraZeneca)	Type 2 diabetes (http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/022350lbl.pdf)	Dipeptidyl peptidase 4 inhibitor	31 Jul (S)
Pitavastatin (Livalo)	Kowa Pharmaceuticals (developed with Daiichi Sankyo and Nissan)	Hyperlipidaemia and mixed dyslipidaemia (http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/022363s000lbl.pdf)	3-hydroxy-3-methylglutaryl-CoA reductase inhibitor	3 Aug (S)
Asenapine (Saphris)	Organon BioSciences (now a subsidiary of Merck)	Schizophrenia and bipolar disorder (http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/022117s000lbl.pdf)	Atypical antipsychotic agent, thought to act through antagonist activity at the dopamine type 2 and serotonin type 2 receptors	13 Aug (S)
Vigabatrin (Sabril)	Lundbeck	Infantile spasms in children aged 1 month to 2 years and complex partial seizures in adults (http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020427s000lbl.pdf)	Mechanism of antiseizure action is unknown, but is thought to result from the drug's action as an irreversible inhibitor of γ-aminobutyric acid transaminase	21 Aug (P, O,S)
Bepotastine besilate (Bepreve)	ISTA Pharmaceuticals (developed with Senju Pharmaceutical)	Allergic conjunctivitis (http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/022288lbl.pdf)	Histamine H_1 receptor antagonist	4 Sep (S)
Telavancin (Vibativ)	Theravance (developed with Astellas Pharma)	Complicated skin and skin structure infections (http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/022110s000lbl.pdf)	Lipoglycopeptide antibacterial agent	11 Sep (S)
Pralatrexate (Folotyn)	Allos Therapeutics	Peripheral T cell lymphoma (http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/022468lbl.pdf)	Folate analogue metabolic inhibitor that competitively inhibits dihydrofolate reductase	24 Sep (P,O)
Pazopanib HCl (Votrient)	GlaxoSmithKline	Renal cell carcinoma (http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/022465lbl.pdf)	A multikinase inhibitor with targets that include vascular endothelial growth factor receptors	19 Oct (S)
Romidepsin (Istodax)	Gloucester Pharmaceuticals	Cutaneous T cell lymphoma (http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/022393lbl.pdf)	Histone deacetylase inhibitor	5 Nov (S)

O, FDA orphan designation; P, FDA priority review; S, FDA standard review. *The company that submitted the original new drug application to the FDA.

to the letter by June 2009, and Kalbitor was approved in November 2009. "Not all delays are associated with REMS, but it may be that the FDA is using this requirement to gain more time in reviewing products," suggests Schmidt. "There were a number of products that were also pushed out of 2009 for reasons related to REMS," adds Jones: "Amgen's Prolia [denosumab], GlaxoSmithKline and XenoPort's Solzira [gapapentin enacarbil] and Acorda's Amaya [fampridine SR]."

During his December 2009 presentation to the FDA–CMS (Centers for Medicare and Medicaid Services) summit, John Jenkins, Director of the Office of New Drugs at CDER, noted that "Incorporating the development and approval of complex REMS during the first review cycle is almost impossible." He added that developers must plan well in advance (at the end of Phase II or before submitting an NDA or BLA) for complex REMS, to allow the possibility for a first-cycle approval of the NDA or BLA.

The effect of REMS on approval times should, however, decrease as industry's experience of REMS increases. "Many companies have now been through the process at least once and, the more experience they gain with REMS, the better they and the regulators are likely to become at minimizing approval delays and post-market risk to patients," says Jones.

Milne agrees, adding that REMS may have the longer-term benefit of getting new drugs to patients faster. "A lot of the work to manage risk in the post-marketing realm is going to pay off in terms of lessening the FDA's risk averseness with regard to approval," he says. "We are starting to see some of the regulatory 'squeeze' easing, which came in after Rezulin [troglitazone, for the treatment of type 2 diabetes] and Vioxx [rofecoxib, for the treatment of pain indications] were withdrawn from the market [in 2000 and 2004, respectively]. Many people couldn't wait for the past decade to go away; I think the next one will be better — a more productive and efficient decade."

Bethan Hughes