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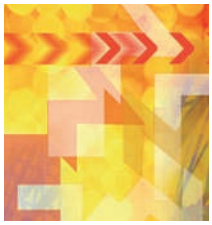

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2008 FDA drug approvals

Specialty products continued to dominate new drug and biologic approvals in the US in a year in which the evolving regulatory environment also featured heavily.

Bethan Hughes

US FDA approvals in 2008 totalled 21 new molecular entities (NMEs) and 3 biologic licence applications (BLAs) that were evaluated by the Center for Drug Evaluation and Research (CDER) (TABLES 1,2). For some, this slight increase in approvals compared with recent years (FIG. 1) is cause for optimism. "It still falls far short of the approval rate seen in the 1990s, and we do need to see more consistency in terms of that number increasing each year, but overall it is encouraging," says Andrew Jones, Senior Pharmaceutical Analyst, Ernst & Young, London, UK.

John Jenkins, director of the FDA's Office of New Drugs (OND), cautions about reading too much into slight changes year to year in the number of approvals. "The fact that we approved a few more one year than we approved in a previous year should not be interpreted as a trend or the FDA speeding up or slowing down; it's simply that those are the applications that met the standards for approval," he says. "Some were applications that went through on one cycle and some are applications that were submitted years ago, requiring multiple cycles. I think you have to keep that in mind when you are looking at the data," he adds.

Indeed, at least four of this year's NMEs and BLAs were delayed from previous years: desvenlafaxine (Pristiq; Wyeth), alvimopan (Entereg; Adolor), lacosamide (Vimpat; Schwarz) and certolizumab pegol (Cimzia; UCB). "Those approvals came with a pound of flesh; at one point they may have seemed in doubt but finally got squeezed out of the FDA's doors. So, in no way do I think that the FDA is an easier place for companies to send their drug applications," says Eric Schmidt, Biotechnology Equity Research Analyst, Cowen and Company, New York, USA.

Ongoing specialty trend

However, there are some situations in which the regulatory process is considered likely to be smoother. "The theme is the same: if you are going for a rare disorder or a very severe disease, such as with Treanda ▸

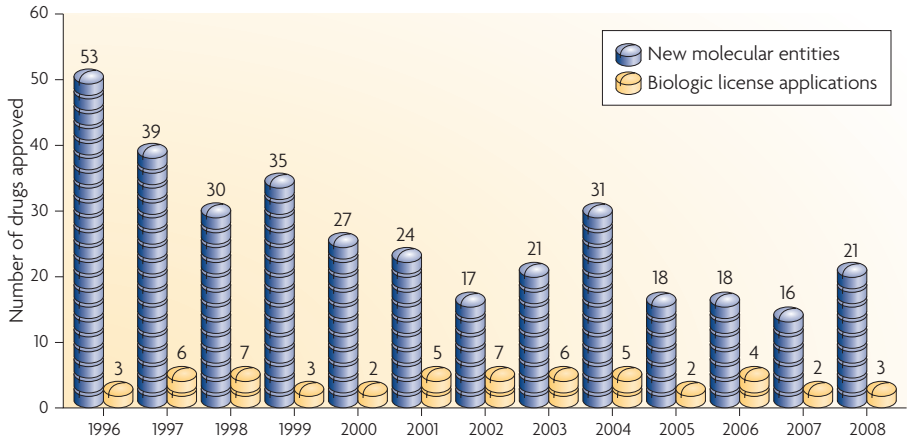

Figure 1 | **FDA drug approvals.** New molecular entities and biologic license applications approved by the US FDA's Center for Drug Evaluation and Research by year.

[bendamustine hydrochloride, developed by Cephalon for chronic lymphocytic leukaemia], you have a better shot at getting the FDA to turn around your application without any delay," says Schmidt. In this case, the new drug application (NDA) for bendamustine hydrochloride, an orphan drug, was submitted in September 2007, received priority status in December 2007 and received approval in March 2008.

This perception of approvals being more straightforward for such products may help explain why the majority of NME and BLA approvals this year were for specialist-care indications, suggests Philip Ma, Director in the Silicon Valley office of McKinsey & Company, USA. Other factors also attract developers to such products, he explains: "The unmet need tends to be relatively high and there's generally less payer pressure than in the primary care areas." In addition, new products tend to be targeted therapies that lend themselves to specialty care, and account for a lot of the R&D of many of the players in this area, says Ma.

Overall, of the NMEs and BLAs approved in 2008, few are anticipated to become blockbusters. But as many of these products come from smaller specialty pharmaceutical or biotech companies, they don't necessarily need to generate this level of revenue, suggests Jones. "For some, the revenue potential that specialty products produce is sufficient to pursue those markets."

Novelty and unmet need

Although the overall number of approvals in 2008 was higher than in 2007 (FIG. 1), the number of agents given priority reviews (TABLES 1,2) — a reflection of their perceived potential to address unmet medical needs — was nine in both years. From the perspective of therapeutic novelty, two products that attracted attention in 2008 were romiplostim (Nplate; Amgen) (TABLE 1) and eltrombopag (Promacta; GlaxoSmithKline) (TABLE 2). These drugs, both of which act as thrombopoietin receptor agonists, are the first two targeted treatments available for thrombocytopenia in patients with chronic immune (idiopathic) thrombocytopenic purpura. In addition, Regeneron's biologic rilonacept (Arcalyst), an interleukin-1β blocker, became the first therapy to be approved for the rare inflammatory cryopyrin-associated periodic syndromes, which involve excessive release of activated interleukin-1β.

Michael Hay, senior analyst at BioMedTracker, Sagient Research Systems, San Diego, USA, highlights the approval of Cinryze (which does not appear in TABLE 1 because it is purified from blood plasma and was therefore approved by the Center for Biologics Evaluation and Research, not CDER), a serum-derived C1-esterase inhibitor developed by Lev Pharmaceuticals. Cinryze is the first product to be approved by the FDA for the routine prophylaxis of angio-oedema attacks in patients with hereditary angio-oedema.

Regulatory delays

Delays in regulatory decisions were also a significant approvals-related trend in 2008 (*Nature Rev. Drug Discov.* 1, 10–11; 2009). It is no secret that in recent years the FDA has been struggling to meet its Prescription Drug User Fee Act (PDUFA) goals to achieve review of 90% of NDAs and BLAs within 10 months for standard reviews and within 6 months for priority reviews. During the fiscal year (FY) 2008 (from October 2007 to September 2008) the FDA made a management decision that they would not be able to meet all PDUFA goals and from 1 January to 31 October 2008 20% (32 out of 159 NDAs and BLAs) were missed (http://www.fda.gov/CDER/present/fda-cms-summit2008/FDA_CMS_Summit_2008_120408.pdf).

Products with delayed PDUFA dates for which regulatory decisions are still pending include two potential blockbusters. For Lilly's prasugrel hydrochloride, which has been developed for the secondary prevention of thrombotic cardiovascular complications in patients with acute coronary syndrome managed with percutaneous coronary intervention, the date was extended from June 2008 to February 2009. And for Takeda's alogliptin, a dipeptidyl peptidase 4 inhibitor for type 2 diabetes, the PDUFA date was extended from October 2008 to June 2009. Although big pharma may be able to bear the financial costs of these delays,

Table 1 | **New biologics approved by the US FDA's Center for Drug Evaluation and Research in 2008**

Generic name (Trade name)	Company*	Indication (URL of label information if available)	Properties	Date
Rilonacept (Arcalyst)	Regeneron	Cryopyrin-associated periodic syndromes including familial cold autoinflammatory syndrome and Muckle–Wells syndrome (http://www.fda.gov/cder/foi/label/2008/125249lbl.pdf)	Interleukin-1 blocker	27 Feb (P, O)
Certolizumab pegol (Cimzia)	UCB	Crohn's disease (http://www.fda.gov/cder/foi/label/2008/125160s000lbl.pdf)	Tumour necrosis factor blocker	22 Apr (S)
Romiplostim (Nplate)	Amgen	Thrombocytopenia in patients with chronic immune (idiopathic) thrombocytopenic purpura (http://www.fda.gov/cder/foi/label/2008/125268lbl.pdf)	Thrombopoietin receptor agonist	22 Aug (P, O)

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

Table 2 | **New molecular entities approved by the US FDA's Center for Drug Evaluation and Research in 2008**

Generic name (Trade name)	Company*	Indication (URL of label information if available)	Properties	Date
Etravirine (Intelence)	Tibotec	HIV-1 (http://www.fda.gov/cder/foi/label/2008/022187lbl.pdf)	Non-nucleoside reverse transcriptase inhibitor	18 Jan (P)
Desvenlafaxine (Pristiq)	Wyeth	Major depressive disorder (http://www.fda.gov/cder/foi/label/2008/021992lbl.pdf)	Selective serotonin and noradrenaline reuptake inhibitor	29 Feb (S)
Bendamustine hydrochloride (Treanda)	Cephalon	Chronic lymphocytic leukaemia (http://www.fda.gov/cder/foi/label/2008/022249lbl.pdf)	Mechlorethamine derivative with DNA-alkylating activity	20 Mar (P, O)
Regadenoson (Lexiscan)	CV Therapeutics	Pharmacological stress agent for radionuclide imaging (http://www.fda.gov/cder/foi/label/2008/022161lbl.pdf)	A_{2A} adenosine receptor agonist	10 Apr (S)
Methylnaltrexone bromide (Relistor)	Progenics	Opioid-induced constipation	Peripherally acting μ opioid receptor antagonist	24 Apr (S)
Alvimopan (Entereg)	Adolor	To accelerate gastrointestinal recovery following bowel resection surgery (http://www.fda.gov/cder/foi/label/2008/021775lbl.pdf)	Peripherally acting μ opioid receptor antagonist	20 May (S)
Difluprednate (Durezol)	Sirion	Inflammation and pain associated with ocular surgery (http://www.fda.gov/cder/foi/label/2008/022212lbl.pdf)	Ocular corticosteroid thought to act by the induction of phospholipase A2 inhibitory proteins	23 Jun (P)
Gadoxetate disodium (Eovist)	Bayer	Gadolinium-based contrast agent (http://www.fda.gov/cder/foi/label/2008/022090lbl.pdf)	Paramagnetic compound	3 Jul (S)
Clevidipine butyrate (Cleviprex)	The Medicines Company	Peri-operative hypertension when oral therapy is not feasible or not desirable	Short-acting dihydropyridine calcium channel antagonist	1 Aug (S)
Tetrabenazine (Xenazine)	Prestwick	Chorea associated with Huntington's disease (http://www.fda.gov/cder/foi/label/2008/021894lbl.pdf)	Monoamine-depleting agent	15 Aug (P, O)
Iobenguane I-123 (AdreView)	GE Healthcare	Radiopharmaceutical agent for the detection of primary or metastatic phaeochromocytoma or neuroblastoma (http://www.fda.gov/cder/foi/label/2008/22290lbl.pdf)	Taken up by the noradrenaline transporter in adrenergic nerve terminals	19 Sep (P, O)
Silodosin (Rapaflo)	Watson	Benign prostatic hyperplasia (http://www.fda.gov/cder/foi/label/2008/022206lbl.pdf)	α1 adrenoceptor antagonist	8 Oct (S)
Lacosamide (Vimpat)	Schwarz	Partial-onset seizures in epilepsy (http://www.fda.gov/cder/foi/label/2008/022253lbl.pdf)	Selectively enhances slow inactivation of voltage-gated sodium channels and binds to collapsin response mediator protein 2	28 Oct (S)
Fesoterodine fumarate (Toviaz)	Pfizer	Overactive bladder disorder (http://www.fda.gov/cder/foi/label/2008/022030lbl.pdf)	Competitive muscarinic receptor antagonist	31 Oct (S)
Rufinamide (Banzel)	Eisai	Seizures associated with Lennox–Gastaut syndrome (http://www.fda.gov/cder/foi/label/2008/021911lbl.pdf)	Sodium channel activity modulator	14 Nov (S)
Eltrombopag (Promacta)	GlaxoSmithKline	Thrombocytopenia in patients with chronic immune (idiopathic) thrombocytopenic purpura (http://www.fda.gov/cder/foi/label/2008/022291lbl.pdf)	Thrombopoietin receptor agonist	20 Nov (P, O)
Tapentadol hydrochloride‡	Ortho–McNeil–Janssen	Moderate to severe acute pain	μ opioid receptor agonist and noradrenaline reuptake inhibitor	20 Nov (S)
Fospropofol disodium (Lusedra)	Eisai	Monitored anaesthesia care sedation (http://www.fda.gov/cder/foi/label/2008/022244lbl.pdf)	Prodrug of propofol	12 Dec (S)
Plerixafor (Mozobil)	Genzyme	Autologous transplantation in patients with non-Hodgkin's lymphoma and multiple myeloma (http://www.fda.gov/cder/foi/label/2008/022311lbl.pdf)	CXCR4 antagonist	15 Dec (P, O)
Gadofosveset (Vasovist)	Epix	Gadolinium-based contrast agent	Paramagnetic compound	22 Dec (S)
Degarelix (Firmagon)	Ferring	Advanced prostate cancer (http://www.fda.gov/cder/foi/label/2008/022201lbl.pdf)	Gonadotropin-releasing hormone receptor antagonist	24 Dec (S)

*The company that submitted the original new drug application to the US FDA. ‡Trade name not available at the time of going to press. O, FDA orphan designation; P, FDA priority review; S, FDA standard review.

smaller companies may not have the finances to ensure that a sales force is ready for launch of a product when it finally achieves approval, suggests Hay.

The reasons that the FDA has given for not meeting PDUFA goals include increased workload, in part related to the FDA Amendments Act (FDAAA) 2007, which introduced new authorities to require post-market studies, safety labelling changes, and risk evaluation and mitigation strategies (REMS). To help ease the strain on the FDA's workload — which was well acknowledged before the FDAAA added to it (*Nature Rev. Drug Discov.* 7, 107–109; 2008) — the FDA has been actively recruiting new employees, and CDER achieved a net gain of 396 staff in FY 2008 with 121 specifically working in the OND.

"It's very good news that we have been able to bring up our staffing levels dramatically. Over time, that will start paying dividends regarding our ability to get back on track with meeting not only our PDUFA goals but also the new provisions under the FDAAA legislation and new paediatric drug development legislation. So it's not just the user fee goals that the new staffing will help us with," says Jenkins. He also adds an important caveat: "It can take 2–3 years for a new reviewer to be fully trained and productive enough to carry a full workload because of the complexity of the work that we do."

> For some, the revenue potential that specialty products produce is sufficient to pursue those markets.

Impact of REMS

There has also been considerable debate regarding the potential impact on approvals of the FDA's authority to require REMS (*Nature Rev. Drug Discov.* 7, 963; 2008). "Some people have questioned whether our ability to require REMS for drugs might lead us to approve drugs that maybe in the past we would not have been willing to approve," says Jenkins. "I think that is a very difficult question to answer because, before REMS, we had the ability to work with companies to develop RiskMAPS [risk minimization action plans, which have been available since 2005]."

Indeed, earlier discussions about safety issues in view of such tools might have helped companies to reduce the possibility of REMS-related delay. "While REMS have the potential to slow an approval, if a REMS had to be put in place, it should have been something that the agency discussed with the sponsor early on and should not have had a major impact on delaying approvals," says Lawrence Liberti, Vice President, CMR International Institute for Regulatory Science, London, UK.

Nevertheless, some still consider that REMS might have slowed some approvals. Of the currently approved REMS (last updated 23 October 2008 (http://www.fda.gov/cder/drug/DrugSafety/REMS.htm)), two are NMEs and two are BLAs that were approved in 2008: alvimopan (Entereg; Adolor), tetrabenazine (Xenazine; Prestwick), certolizumab pegol (Cimzia; UCB) and romiplostim (Nplate; Amgen). Three of these products experienced regulatory delays that have been attributed in part to the sponsor having to meet the requirement for adequate REMS.

From an investor perspective, REMS have an additional negative impact on commercial prospects. "I think that the commercial marketplace for a drug can be constrained by a REMS programme. Nplate from Amgen is an example of a very stringent REMS programme that could make it more difficult for prescribing," says Schmidt.

For sponsors developing products, Jenkins thinks that risk management should be incorporated into drug development programmes as early as possible. "Some of the REMS are very complicated to put together, and by that I mean something that has elements to assure safe use and has restricted distribution. It can take months to develop a programme and interface with us to reach an agreement. So, if you wait until the end for an application that is going to need that type of REMS then you are setting the whole process back by several months at least." Early consideration of risk management may also help sponsors find ways to identify patients at risk of side effects that could be incorporated into the clinical development programme, he adds.

Advisory panels and guidance

Given another FDAAA 2007 requirement that all new chemical entities are referred to an advisory committee unless the FDA determines otherwise, both Hay and Schmidt expect to see a continued increase in the number of advisory panels. "That also could have contributed to some delays," says Hay, "particularly as the conflict of interest rules about who can be on the advisory panels can make it complicated to get through a review process." The difficulty of assembling advisory panels is thought to have contributed to the delay for alogliptin.

Another reason for the postponement of the alogliptin PDUFA date could be related to the FDA's recent announcement that manufacturers developing new drugs and biologics for type 2 diabetes will have to provide evidence that the therapy will not increase the risk of cardiovascular events such as a heart attack (see page 99). Some insight into how such guidance could be applied might come from an advisory panel meeting in March 2009 to discuss Novo Nordisk's diabetes drug liraglutide, a glucagon-like peptide 1 analogue. "The meeting will be interesting because the cardiovascular guidance was not available at the time liraglutide's Phase III studies were conducted and this will be the first panel for a diabetes drug since the new guidelines came out," says Hay.

> Risk management should be incorporated into drug development programmes as early as possible.

Upcoming regulatory decisions

In addition to the pending decisions for delayed products such as alogliptin and prasugrel, analysts are interested in Amgen's denosumab, a potential blockbuster for osteoporosis. There are also a few NDAs and resubmissions that are eagerly awaited. The first is Dendreon's sipuleucel-T (Provenge), for advanced prostate cancer, for which final results of the additional efficacy data required by the FDA's approvable letter in May 2007 should be available by mid 2009. "You could see that as a PDUFA by the end of this year," says Hay.

Another NDA of broad interest that is anticipated to be filed early in 2009 is for Mannkind's inhaled insulin. "Most companies dropped their inhaled insulin programmes following the withdrawal of Exubera [Pfizer]," says Hay. "Mannkind's data look good but no-one knows what to do with the lung cancer data that came up with Exubera, so it will be very interesting to see how the FDA addresses that issue." Such issues are among the many that will be faced by the new FDA Commissioner, who, although not yet appointed at the time of going to press, is hoped by many to take up the role as early as possible in 2009.