Fresh from the biotech pipeline—2011

Drug approvals were up in 2011, reversing the trend of the last decade. Jim Kling reports.

The numbers looked good in 2011 for the US Food and Drug Administration (FDA). At the end of the fiscal year (September 30), the agency announced with some fanfare that it had approved 34 new molecular entities. That number tops all other performances of the past decade, with the exception of the 2007 fiscal year, which saw 37 approvals (**Fig. 1**). The agency was also faster in handing down decisions, completing priority reviews on average in 6 months and standard reviews in 13. "I'm not sure they can do much better on standard reviews," says George Zavoico, managing director for equity research for the New York–based investment bank MLV.

The year saw several first-in-class drug approvals, addressing some long-standing unmet medical needs, and two accelerated approvals for biologics. Even so, the agency continued to be bedeviled by high-profile controversies, which are likely to reverberate in the coming year. The decision to rescind accelerated approval of Genentech's Avastin (bevacizumab) for metastatic breast cancer after an unprecedented series of hearings brought a deluge of complaints from physicians and patients who saw clinical benefits from the drug. And the year ended on a sour note for the agency with the controversial reversal by the secretary of the Department of Health and Human Services of a decision by the FDA to make an emergency contraceptive available to all women of reproductive age.

Inching toward follow-ons

No guidelines were issued for follow-on biologics (referred to as biosimilars by the FDA) in 2011, although there were some encouraging signs. Biosimilars continue to be an important topic of conversation between the agency and the biotech industry, as they were at a public meeting in December to discuss user fees for applications for the 2013 through 2017 fiscal years. In January, the agency announced that it had "completed recommendations" for three user fee programs, among them new fees for generics and biosimilars for PDUFA V, which comes up for renewal this year.

"We've seen work in progress on the biosimilars front and it does appear that something will be coming out sooner rather than later," says Matthew Hudes, US managing principal for biotech at New York–based Deloitte Consulting. "The main issue they're dealing with is, 'How similar is similar enough?'" With biologics, it's not just the chemical makeup of the drug but also the three-dimensional structure, post-translational modifications, and protein aggregation that can affect how the drug affects the body. "It's about understanding how to measure immunogenicity and to build that into the kinds of studies that will be done. FDA has to provide leadership on that question," says Hudes.

Some companies have already approached FDA about biosimilars, though the agency has declined to identify them. "It's clear that people aren't waiting for all this; they're moving ahead. My guess is the first biosimilars will be approved in 2013 or early 2014," says Christopher Ohly, a partner at Schiff Hardin in Washington, DC.

Interest isn't coming just from larger generics companies, but also generics divisions of big pharma and even some of the larger traditional biologics manufacturers as well, which might surprise some, according to Hudes. "A biosimilar will be neither cheap nor easy to get through the approval process, so the level of expertise will be critical," he says.

Still unanswered is the question of how different a biologic can be from the original before it is no longer a biosimilar, but a 'biobetter' that requires a new biologics license application. Biobetters may be part of the new biosimilars pathway, or they may be left out altogether, according to Ohly. "As companies go through the biosimilar process or, more importantly, the interchangeable-drug process [which allows pharmacists to automatically substitute a generic for an innovator product prescription], they'll attempt to engineer products that are not only similar but have reduced immunogenicity and higher potency. I think the biosimilar process will turn into an innovation process, whether that innovation is the result of action by a reference product sponsor, an originator or by a biosimilar developer," he says.

Despite ongoing discussions, FDA is clearly lagging behind Europe, which has already approved more than a dozen biosimilars[1]. That slow pace of implementation has encouraged companies to introduce them in regions or countries where the oversight is less stringent, such as India or China. "When you look at it from a societal standpoint, what [the FDA has] done is [make the US healthcare providers] the last beneficiaries, and we're going to have the highest cost, at least for awhile," says Ohly.

Nonetheless, many remain optimistic that the agency will move quickly on biosimilars in the coming year or so. "We know they're working really hard on it, trying to get the user fee system in place, and everybody agrees they need to be properly funded because this will put a significant burden on the resources of the review team," says David Fox, a partner in the FDA group at Hogan Lovells in Washington, DC. "I think that will settle out in the next year to 18 months," adds Hudes.

Twenty-first century challenges

The common criticism that the agency is too risk averse in terms of the drug approval process continued to concern companies and their investors, following high-profile market withdrawals over safety issues and late-stage failures, particularly in areas such as obesity drugs. "We know there are folks at the agency who are

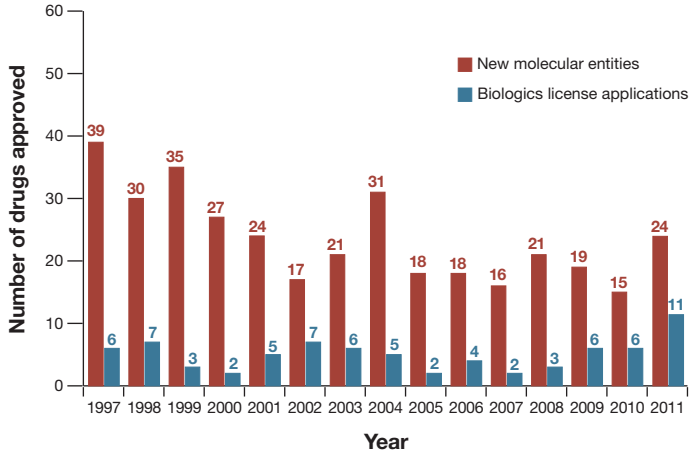

Figure 1 FDA new molecular entities and biologics license application approvals, 1997–2011.

visionary and very committed to helping new therapeutics reach patients, but it seemed like they were overwhelmed [by food safety scares and risk aversion] early in the year," says Hudes. And although there were some positive effects of money coming in through Obama's stimulus package in terms of hiring more personnel, underfunding continues to be a major issue for the agency.

But other issues are starting to rear their heads, for example, the issue of comparative effectiveness. After a meeting of the FDA Endocrinologic and Metabolic Drugs Advisory Committee in May last year, which reviewed data on Tricor (fenofibrate) given with a statin in diabetic patients (the ACCORD-Lipid trial run by the US National Heart, Lung and Blood Institute), Deerfield, Illinois–based Abbott Pharmaceuticals was told it would now have to conduct a large clinical study to show whether Tricor and a statin had a better outcome compared with statin alone. The question this raises is whether other companies will now find FDA obliging them to run large trials on important drug franchises on the basis of comparative trial data.

Industry also continues to find itself two or three steps ahead of the agency when it comes to using information technology and other high-tech tools to advance personalized medicine, according to Hudes. "The industry is far outstripping the agency," he says. Draft guidance for companion diagnostics was finally issued in September last year, but many companies complain that the agency's inexperience in handling personalized treatments remains one of the hurdles to development of these types of drugs.

In terms of the internet, the agency finally issued marketing guidelines for social media, which came after a two-year wait and still leaves many questions unanswered. "If you're waiting for divine guidance, you're still waiting," Peter Pitts, president of the Center for Medicine in the Public Interest, was quoted as saying[2]. "FDA has made it very clear they were not going to make platform-specific guidelines, like how to use Facebook, how to use Twitter, because social media evolves every day," he added.

Although with the FDA commissioner Margaret Hamburg at the helm and the Obama administration purporting to put science before politics, pressure from inside the Beltway appears to have been consequential in 2011. Genetically modified fish remain in limbo, following the intervention of politicians from the Pacific Northwest (**Box 1**). And the reversal by the Department of Health and Human Services secretary Kathleen Sebelius of the FDA's decision on an emergency contraceptive has people scratching their heads. "The idea that there is political influence on the FDA approval process…people start questioning the motivations when they see a decision like this. I was surprised that everybody wasn't on the same page. It was a little embarrassing," says David Rosen, head of Foley & Lardner's FDA practice and co-chair of the Boston firm's life sciences industry team.

2011 honor roll

Eleven biologics were approved in 2011 (**Table 1**) on a par with previous years' approvals. In terms of biologics, "it wasn't a landmark year," according to Richard Hendriks, a senior analyst at the Tolland, Connecticut–based consultancy Nerac. "There were a lot of typical (approvals) in the biologics arena." In addition, a record number of biopharmaceutical approvals were for orphan indications, which portends a low economic impact, even as they represent an advance for a small number of patients. A burst in orphan drugs was expected, following the impressive market performance of orphan drugs like Genzyme's Cerezyme (imiglucerase) 10–15 years ago (Cerezyme was approved in 1994). "Some saw an opportunity and jumped into the orphan market," says Ron Rader, president of the Biotechnology Information Institute of Rockville, Maryland. Rader also notes in his annual survey of biopharmaceuticals, a number of companies enjoying their first approvals in 2011, as well as the first approval of a biopharmaceutical made outside the US[3]. "Another trend—the internationalization of biopharmaceutical production—[is] coming to fruition," says Rader, (Anascorp, an immunoglobin for scorpion bites, manufactured by Bioclon in Mexico was among several other drugs coming in from overseas manufacturers) .

Yet several notable drugs grace this year's crop of approvals: two drugs for metastatic melanoma, an antibody-toxin conjugate for two undertreated lymphomas, two drug–companion diagnostic combinations and the first new drug for lupus in nearly a half-century.

Adcetris (brentuximab vedotin). After a series of setbacks for other immunoconjugates, the field of antibody-drug conjugates received a boost with the August approval of Adcetris, developed and marketed by Bothell, Washington–based Seattle Genetics. This drug now represents the only approved antibody conjugate since the voluntary withdrawal of Mylotarg (gemtuzumab) by its developer Pfizer in 2010. The chimeric human-mouse monoclonal antibody (mAb) conjugated to auristatin, a microtubule-disrupting agent, targets the CD30 receptor on the surface of lymphoma cells. After binding to CD30, the antibody is internalized along with the toxin auristatin E. It was approved for Hodgkin's lymphoma and the rare systemic anaplastic large cell lymphoma.

The drug was approved under the agency's accelerated approval program, which is rare, though not unheard of, for a single-arm study[4]. But the high response rate (73% in one indication, 86% in the other) led to a unanimous decision by the FDA's Oncologic Drugs Advisory Committee for approval. The drug will be prescribed for Hodgkin's lymphoma patients whose disease has progressed after autologous stem cell transplant or who have undergone two chemotherapy treatments and are ineligible for a transplant.

"They ran the appropriate studies to get those compounds into really niche lymphoma indications. People have always questioned whether conjugates are better than naked antibodies, and the answer is hugely positive," says Fong.

Box 1 Genetically modified fish still adrift

The developers of genetically modified salmon, Waltham, Massachusetts–based Aqua-Bounty, entered 2011 with high hopes of a final approval that never came. The AquAdvantage genetically modified salmon is an Atlantic species that has been bolstered with regulatory sequences derived from the Chinook salmon found in the Pacific Ocean. It reaches the same weight as commercial salmon, but does so in half the time.

The fish, which has been in development since 1995, was reviewed as a drug instead of a food. When the agency released a draft guidance in 2008 for transgenic animals, optimism grew that the fish would be cleared. But political pressure has continued to stymie the review process. Last July, eight senators from Pacific coast states with strong fishing industries wrote a letter to FDA insisting that it halt its review of AquAdvantage, citing threats to jobs and the environment, and threatening legislation to de-fund the agency's review of the fish if it didn't comply. The FDA took no further regulatory action during 2011.

AquaBounty insists that the salmon are environmentally safe because the fish are all female and 99.8% triploid and thus infertile. The company also asserts that the fish are to be grown in Panama, far away from their native waters and thus unlikely to be a threat to interbreed with wild populations. *JK*

Table 1 2011 biologics approvals

Brand name	Generic name	Indication	Type of drug	Developer
Actemra	Tocilizumab	Systemic juvenile idiopathic arthritis	Humanized mAb	Genentech
Adcetris	Brentuximab vedotin	Hodgkin's lymphoma and anaplastic large cell lymphoma	Chimeric human-mouse mAb conjugate	Seattle Genetics
Benlysta	Belimumab	Systemic lupus erythematosus	Human mAb	Human Genome Sciences
Erwinaze	Asparaginase *Erwinia chrysanthemi*	Acute lymphoblastic leukemia	Enzyme derived from *Erwinia chrysanthemi*	EUSA Pharma
Eylea	Aflibercept	Age-related macular degeneration	Fusion protein of portions of VEGF receptors 1 and 2 fused to the Fc portion of IgG	Regeneron
Hemacord	Hematopoietic progenitor cells from human cord blood	Bone marrow transplant; stem cell transplant	Allogeneic cord blood hematopoietic progenitor cells	New York Blood Center
IaViv	Azficel-T	Nasolabial fold wrinkles	Autologous cellular product consisting of patient's collagen-producing fibroblasts	Fibrocell Science
Nulojix	Belatacept	Transplant rejection	Fusion protein of Fc fragment of human IgG1 linked to the extracellular domain of CTLA-4	Bristol-Meyers Squibb
Soliris	Eculizumab	Atypical hemolytic uremic syndrome	Humanized mAb	Alexion
Sylatron	Peginterferon alfa-2b	Melanoma	Conjugate of recombinant alfa-2b interferon with monomethoxy polyethylene glycol	Merck
Yervoy	Ipilimumab	Melanoma	Humanized mAb	Bristol-Myers Squibb

Benlysta (belimumab). The approval in March of Benlysta for systemic lupus erythematosus, manufactured by Human Genome Sciences of Rockville, Maryland, partnered with London's GlaxoSmithKline, was met with euphoria by patients and their doctors. The last drug to be approved for this condition was Plaquenil (hydroxychloroquine; Sanofi-aventis of Paris), which gained approval in 1955 for lupus and malaria.

Benlysta, a humanized mAb, targets B-lymphocyte stimulator, which drives autoantibody production in lupus. Two phase 3 clinical trials supported the application. In one trial, 58% of patients on Benlysta plus standard therapy met the primary endpoint of reduction in lupus disease activity, compared to 44% of those on standard therapy and placebo. In the other trial, the numbers were 43% and 34%, respectively[5].

Lupus patients currently rely on nonsteroidal anti-inflammatory drugs, corticosteroids and immune suppressants for symptom relief. "[Benlysta] was a pretty seminal drug because of that indication. It's such a difficult [disease] to treat," says Fong, though he also notes that the drug has underperformed so far. "There are some questions about marketability and how doctors are using [Benlysta] in a clinical setting."

Jakafi (ruxolitinib). The first Janus-associated kinase (JAK) inhibitor, Jakafi, got the nod in November for the treatment of a rare blood cancer, myelofibrosis and other myeloproliferative disorders. The drug was developed by Incyte in partnership with Novartis, of Basel, and represents the first approval for the Wilmington, Delaware–based biotech. The JAK signaling pathway operates through multiple cytokines and growth factors to stimulate cell proliferation and migration, and differentiation, among other processes, giving inhibitors of JAK kinases the power to affect multiple signaling pathways. Jakafi inhibits JAK1 and JAK2, whose signaling processes are believed to be disrupted in myelofibrosis. This approval process took a mere six years from the time an activating JAK2 mutation was tied to the disease, helped along by the use of a novel patient-reported outcome tool (conducted under a special protocol assessment). Patients in one of the two pivotal phase 3 trials entered symptoms daily into an electronic diary, which was linked to a database. Other companies are developing JAK inhibitors for cancers and inflammatory diseases[6].

Eylea (aflibercept). This recombinant decoy receptor, approved in November, thrust Tarrytown, New York–based Regeneron Pharmaceuticals into the wet age-related macular degeneration market. The protein, which comprises portions of vascular endothelial growth factor (VEGF) receptors 1 and 2 extracellular domains fused to the Fc portion of human IgG1 protein, binds VEGF-A and placental growth factor. Clinical trials demonstrated that it performed as well as the standard of care, Genentech's mAb fragment Lucentis (ranibizumab). Regeneron will price the drug lower, however, which, together with the drug's potential to require fewer injections and less patient monitoring, may allow market penetration. Other potential indications include central retinal vein occlusion and diabetic macular edema, as well as cancer.

Yervoy (ipilimumab). In March, FDA approved Yervoy, manufactured by Bristol-Meyers Squibb of New York. The human mAb blocks the cytotoxic T-lymphocyte antigen 4 receptor on T cells, a modulator of T-cell activity, which acts in antagonism with T-cell stimulator CD53. Yervoy tips the balance in favor of T-cell activation to prompt an immune response against tumors.

In a study presented at the American Society of Clinical Oncology (ASCO) meeting in June 2011, the drug improved overall survival in metastatic melanoma when combined with the drug dacarbazine compared to dacarbazine alone. Survival rates were higher for three years running—47.3% versus 36.3% after one year, 28.5% versus 17.9% at year two and 20.8% versus 12.2% in the third year[7].

The drug is not without drawbacks, however. In clinical trials, 13% of patients experienced severe or fatal autoimmune reactions. For this reason, Yervoy was approved contingent upon a risk evaluation and mitigation strategy.

The approval marks the second year in a row that FDA has approved a cancer immunotherapy. In 2010, the agency approved Dendreon's Provenge (sipuleucel-T), an autologous cell–based therapy for metastatic prostate cancer that involves priming *ex vivo* a patient's white blood cells with a prostate antigen fused to an immune cell activator. With these two decisions, "FDA is signaling that cancer immunology is very much in play," says MLV's Zavoico.

Zelboraf (vemurabenib). Advanced melanoma patients received more good news with the approval in August of Zelboraf, manufactured by Genentech. The drug targets a mutated BRAF protein, which disrupts cell regulation and promotes tumor growth.

In a study announced at the June ASCO meeting, patients treated with Zelboraf alone had significantly improved rates of survival after six months (84% versus 64% of patients on

chemotherapy), which represents a 63% reduction in risk of death compared to patients on chemotherapy.

Together with Pfizer's Xalkori (crizotinib), which was approved with a fluorescent *in situ* hybridization test for detecting rearrangements of the anaplastic lymphoma kinase (*ALK*) gene for non–small cell lung cancer patients with tumors containing *ALK* structural variants, Zelboraf is an example of a combined drug-diagnostic approval. In this case, Zelboraf was approved with a multiplex PCR-based diagnostic for the *BRAF* V600E gene for individuals with advanced melanoma harboring the mutation. The label requires a positive result for a patient to be eligible for the drug.

"[Zelboraf was an] important decision because of what it signaled in terms of personalized medicine, with the diagnostic built into the drug approval. It requires the agency to have two of its centers [the Center for Drug Evaluation and Research and the Center for Devices and Radiological Health] working together closely towards the approval of a product," says Fox.

Accelerated approval under scrutiny

In November, FDA confirmed that it would revoke the approval of Avastin (bevacizumab) for the treatment of metastatic breast cancer. The human mAb, marketed by Genentech and still approved for colon, lung, kidney and brain cancer, targets the VEGF-A, preventing the growth of new blood vessels. After receiving accelerated approval in 2008 based on surrogate endpoints (progression-free survival), the program ran into trouble in 2011 when confirmatory trials failed to show a survival benefit, while causing some serious side effects.

The decision to withdraw approval of Avastin for breast cancer sent a strong message. "It was another validator of the agency's directional impetus to look at overall survival benefit versus progression-free survival, which is a shift that they've been talking a lot about," says Fong.

Whereas some were surprised by the decision because Avastin was widely prescribed, Rosen applauds it. "They went by the rules of the accelerated approval program. You get progression-free survival early on in the process by looking at surrogate markers, and you agree to clinical endpoints, and if you don't meet the endpoints you get an expedited withdrawal," he says.

The issue has put the FDA into an uncomfortable position, especially when it comes to benefits that can be subjective. Progression-free survival may not translate to overall survival, but it might improve a patient's quality of life. "Some would argue that the agency is being overprotective based on aggregate data and not deferring enough to the judgment of the physician," says Fox.

The decision could have consequences for upcoming clinical trials, according to Zavoico. He believes that the agency might be tempted to lessen the risk of having future high-profile withdrawals by requiring more overall survival data and allowing fewer approvals based on progression-free survival. "Unfortunate…I think [progression-free survival] is a pretty good surrogate," Zavoico says.

Looking ahead

2012 might be shaping up to be another good year for biotechs, as they continue to play a major role in new drug applications. "Of 200 compounds in registration, about two-thirds involved alliances with a biotech, so there was a great deal of partnering that was boosting the pipelines of large pharma," says Deloitte's Hudes. Some of the most promising in the pipeline target some new biological mechanisms.

Genentech's vismodegib, which has a March Prescription Drug User Fee Act date, would be a landmark if approved, as it would be the first drug targeting the hedgehog pathway, which plays a central role in embryonic development and becomes reactivated in some cancers. Genentech is targeting basal cell carcinoma, the most common form of skin cancer. It is typically treated surgically, but in its advanced state, it can become disfiguring and even life-threatening and is currently untreatable. The hedgehog pathway may play a role in a number of other cancers, and is in earlier-stage trials for bone, pancreatic and brain cancer.

This year could also see the first therapy approved for cystic fibrosis (CF) that targets the underlying cause: defective or absent fibrosis transmembrane conductance regulator (CFTR) protein, which disrupts the flow of salt and water across membranes in various organs. When the mutated protein is present in the lungs, it leads to abnormally thick mucus that leaves patients vulnerable to infections and progressive lung damage.

Ivacaftor (Kalydeco), developed by Cambridge, Massachusetts–based Vertex Pharmaceuticals, targets the so-called gating defect, most commonly caused by missense mutations, which leaves CFTR proteins nonfunctional. The drug interacts with the membrane protein, prompting the channel to remain open longer to improve the transport of chloride ions across the cell membrane. About 4% of CF patients are believed to have the particular mutation targeted by ivacaftor, the G551D mutation, and would thus be eligible for the drug.

Elsewhere, Protalix BioTherapeutics of Carmiel, Israel, in partnership with Pfizer, is aiming for a 2012 approval of taliglucerase alfa, a recombinant human glucocerebrosidase made in carrot cells. The drug is a treatment for Gaucher disease, a lysosomal storage disorder characterized by an absence of glucocerebrosidase, which normally breaks down the fat glucocerebroside. In the enzyme's absence, lipids accumulate in cells and may lead to spleen and liver enlargement, anemia, bone disease and other symptoms.

Taliglucerase alfa will compete with two recombinant enzymes already on the market, but with some distinct advantages. The other products—Genzyme's Cerezyme and Shire's Vpriv (velaglucerase alpha)—come with a hefty price tag (>$200,000/year for Cerezyme), which Protalix is sure to beat. In addition, both of the other products are manufactured in mammalian tissue culture, which makes them vulnerable to contamination. A problem with Genzyme's production led to worldwide shortages of the enzyme for the past two years.

Another drug hoping to grab a slice of an existing market is carfilzomib, a proteasome inhibitor. Targeting the proteasome, one of the cell's primary mechanisms to dispose of excess or misfolded proteins, was pioneered by Cambridge, Massachusetts–based Millennium Pharmaceuticals' Velcade (bortezomib). This year could see the first next-generation drug approved in the form of S. San Francisco–based Onyx's carfilzomib. Like its predecessor, the drug targets multiple myeloma.

Carfilzomib is purported to be more selective than Velcade, a boronic acid–modified tripeptide that interferes with some proteases, and can lead to neurotoxicity. Both drugs operate on the principle that some cancer cells, particularly in multiple myeloma, overproduce proteins. Interfering with the cell's ability to dispose of the unwanted proteins can be toxic. The proteasome could also play a role in treatment of other cancers because some evidence suggests that blocking protein degradation could lead to the build-up of pro-apoptosis signals.

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