2010 in reflection

From health-care reform to rare diseases, Asher Mullard looks back at some of the key events and themes of 2010.

The year 2010 was yet another difficult 12 months for the pharmaceutical industry. Austerity measures around the world drove down health-care budgets, and the 'patent cliff' steepened, threatening to cost the industry another US$32 billion in sales next year alone (see page 12). As in previous years, companies responded through mergers and acquisitions, deal-making (BOX 1) and sweeping job cuts — over 50,000, according to one estimate[1]. Drug safety also remained a prominent issue: the ongoing saga of cardiovascular concerns with GlaxoSmithKline's diabetes drug rosiglitazone (Avandia), in particular, culminated with the drug being severely restricted in the United States and withdrawn in the European Union. But there were, nevertheless, some positive themes as well. Even health-care reform, a development that had been viewed as a major potential threat for industry, was not as bad as had been expected.

No pain, no gain

After months of debate, horse trading and political positioning, US President Barack Obama signed wide-ranging health-care reform into US law on 23 March 2010. The trade group Pharmaceutical Research and Manufacturers of America (PhRMA) lobbied hard to influence the scope of change, and succeeded, says Business Insights analyst George Green. "In the long term, I think the health-care reform is positive for the industry," he says. "The outcome could have been much, much worse."

In an 82-page report on the overhaul[2], Green argues that the new health-care system will cost the pharmaceutical industry $119 billion in revenue from 2010 to 2019, primarily through discounts on drugs and fees on earnings. But, he counters, these losses will be offset over the second half of the decade by increased access to 32 million patients, resulting in a net upside for the industry of $19 billion by 2019.

Although the near-term hit will hurt, he adds, the effects on research and development (R&D) will be subtle, driven primarily by changes to the future profitability of different therapeutic areas. Drugs that are subject to high pricing pressure — such as antipsychotics and antiretrovirals that will be heavily rebated by the pharmaceutical industry through Medicaid, a health-care scheme for individuals on low income — may fall out of favour. Vaccines and preventive treatments that insurers will have to provide to consumers at no out-of-pocket cost, by contrast, could receive a boost.

Key successes for the industry in the negotiations included provisions blocking Medicare, which provides federal health insurance to those aged 65 years and over, from negotiating drug prices. Three thousand small biotechnology firms also received nearly $1 billion dollars in tax credits in the first round of the newly introduced Qualifying Therapeutic Discovery Project Program. Many hope the scheme will be extended and expanded next year.

Path emerges for biosimilars

Another point scored by the industry in health-care reform came within the terms of the Biologics Price Competition and Innovation Act, which created the long-awaited abbreviated pathway for the approval of biosimilars. Although these follow-on products will eventually exert pricing pressures, the act guaranteed 12 years of data exclusivity for pioneer biologics (see page 23), whereas generics firms had been lobbying for just 5 years of protection.

The full effects of the US's biosimilar pathway, such as how widely it will open the door to competition — particularly for more complex biologics such as monoclonal antibodies — remains unclear. The US Food and Drug Administration (FDA) did, however, gather stakeholders in November to voice their views on what the route should entail[3]. Among the key questions were: are our analytical tools sufficient to establish biosimilarity on a physicochemical level for different classes of product? What type, size and number of clinical trials will be sufficient to support approvability? And how will the agency consider the potential for extrapolation of data between indications?

Many observers expect the FDA to take a case-by-case approach with flexible guidance for the different classes of biologics — much in the same way that the European Medicines Agency (EMA) has proceeded since it first introduced its abbreviated biosimilars route back in 2005 (in November 2010, the EMA's Committee for Medicinal Products for Human Use approved draft guidance specific to monoclonal antibody biosimilars; http://go.nature.com/rxFFaB). As companies wait for a clear pathway to emerge in the United States, potentially over the course of 2011, several are proceeding with plans to submit their follow-on biologic products using standard biologic license applications.

Adapting to change

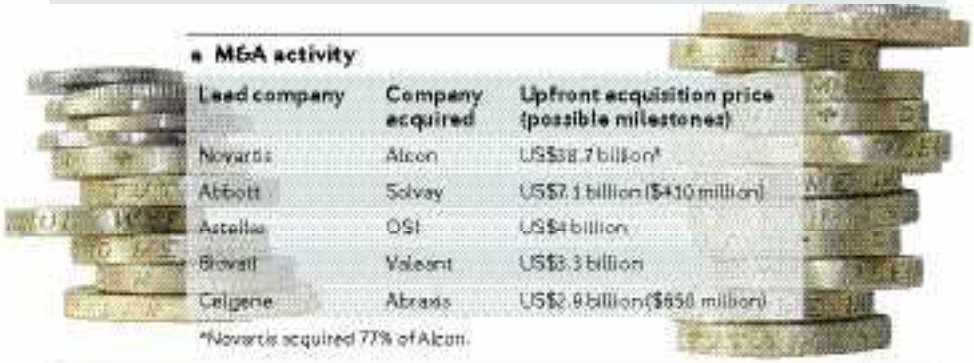
Driven in part by the FDA's publication of another draft guidance, adaptive trial design also received a lift last year. "No doubt 2010 will be regarded as a landmark in the history of adaptive clinical trials," says Donald Berry, a biostatistician at the University of Texas MD Anderson Cancer Center in Houston, USA, who has been spearheading the field of Bayesian clinical trials.

The approach provides the flexibility to modify aspects of ongoing blinded trials, such as population size or the relative allocation of a particular therapy or dose into different arms of a trial, while maintaining statistical validity. This could help accelerate trials and enable sponsors to gain information more effectively from enrolled patients. In the much-awaited draft guidance, the FDA identified key issues for consideration in the design of such trials and recommended the types of information that need to be collected and submitted to facilitate FDA review (http://go.nature.com/lpc5T8). Although the document leaves some questions unanswered, it provides a degree of certainty that observers hope will enable the field to move forward[4].

Indeed, drug makers are increasingly putting their weight behind adaptive trials. "During the year, virtually every major pharmaceutical company at least experimented with Bayesian adaptive designs, and some companies adopted this approach in a major way," says Berry. The Biomarkers Consortium, a public–private partnership that unites the US National Institutes of Health ▸

Box 1 | **Top deals**

In the hopes of softening the blow of the looming patent cliff and of bolstering weak pipelines, drug makers have continued to buy up smaller firms and to license promising drug candidates. Although the number of such transactions is down form the heady, pre-credit-crisis days of 2007, there are indications that they are on the rise[16]. BioMedTracker analysts prepared a list of the top merger and acquisition (M&A) and licensing activity (see part **a** and **b** of the figure, respectively) in 2010. Deals that are still being negotiated, such as Sanofi–Aventis's bid for Genzyme and Johnson & Johnson's bid for Crucell, are not included in the list.



a M&A activity

Lead company	Company acquired	Upfront acquisition price (possible milestones)
Novartis	Alcon	US$38.7 billion*
Abbott	Solvay	US$7.1 billion ($410 million)
Astellas	OSI	US$4 billion
Biovail	Valeant	US$3.3 billion
Celgene	Abraxis	US$2.9 billion ($650 million)

*Novartis acquired 77% of Alcon.

b Licensing deals

Lead company	Licensing company	Product (indications)	US biodollars (upfront; possible milestones)
Rigel	AstraZeneca	Fostamatinib (RA, oncology, SLE, ITP)	$1.24 billion ($100 million; $1.145 billion)
TransTech	Forest Laboratories	TTP399 (type 2 diabetes)	$1.155 billion ($50 million; $1.105 billion)
Orexigen Therapeutics	Takeda	Bupropion plus naltrexone (obesity)	$1.05 billion ($50 million; $1 billion)
Synosia	UCB	Cridadin (Parkinson's disease)	$745 million ($20 million; $725 million)
Quark	Novartis	QPI-1002 (renal disease/renal failure, kidney transplant rejection)	$680 million ($10 million; $670 million)

ITP, idiopathic thrombocytopaenic purpura; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

and pharmaceutical companies, for instance initiated the headline-grabbing I-SPY2 breast cancer trial in March. Using a combination of both biomarkers and adaptive trial design principles, it will test five drugs from three manufacturers — Abbott's veliparib, Amgen's conatumumab and AMG386, and Pfizer's figitumumab and neratinib — as adjuncts to chemotherapy. Confidence in the potential of such strategies was also raised in April by data from the BATTLE trial, which showed that biomarkers can be used in an adaptive design context to guide the treatment of patients with non-small cell lung cancer (NSCLC)[5].

Racing to the market

Some of the year's most groundbreaking clinical results also came from other oncology trials. Pfizer's crizotinib, in particular, made waves. Initially developed as an inhibitor of the tyrosine kinase MET, crizotinib also acts against ALK. When genetic rearrangements in *ALK* were reported in some lung cancers in 2007, researchers decided to test the drug in a genetically selected population. As reported in the *New England Journal of Medicine* in October, around 90% of crizotinib-treated *ALK*-positive patients with NSCLC experienced either an overall response (57%) or stable disease (33%), compared with 10% of patients in historical controls[6]. These Phase I results prompted the initiation of a Phase III trial. Also, Bristol-Myers Squibb subsidiary Medarex's immunotherapy ipilimumab, a monoclonal antibody against cytotoxic T lymphocyte-associated antigen 4, attracted attention, demonstrating impressive survival data in a Phase III advanced melanoma trial (see page 10).

Following Phase III trial successes, telaprevir and boceprevir — two members of a new class of oral drugs for hepatitis C virus (HCV) that inhibit the viral NS3 protease — are racing towards approval in 2011 for a possible multibillion dollar market. Because the current standard HCV treatment — 48-weeks on the generic antiviral ribavirin and interferon conjugated to polyethylene glycol — has only a 50% cure rate and an arduous side-effect profile, there are high hopes for these drugs[7]. Both telaprevir and boceprevir (developed by Vertex/Tibotec and Merck, respectively) performed well in treatment-naive populations (eliciting sustained virologic response (SVR) rates of 63–75%) and in treatment-experienced patients (SVR rates of 59–66%).

The race to develop alternatives to the oral anticoagulant warfarin, another potential multibillion dollar market, also heated up in 2010. Warfarin has been the standard of care for a range of indications, such as stroke prevention in atrial fibrillation (SPAF), for many years, but its use is limited by a narrow therapeutic window and variability in treatment response, necessitating regular monitoring. Consequently, several companies have been developing simpler alternatives, with SPAF considered as a key market[8].

October 2010 saw the FDA approval of one of these drugs — Boehringer Ingelheim's direct thrombin inhibitor dabigatran (Pradaxa) — making it the first new oral anticoagulant to reach the US market in more than 50 years. Dabigitran, which is already approved in Europe for the prevention of venous thromboembolism (VTE) following orthopaedic surgery, was approved in the United States for SPAF based on the 18,113-patient RE-LY trial, reported in 2009, which showed that it was non-inferior to warfarin[9]. Data from other contenders are keeping the competition interesting, however. In November, Bayer/Johnson & Johnson's pivotal ROCKET-AF trial showed that the oral factor Xa inhibitor rivaroxaban (Xarelto) is also non-inferior to warfarin. Rivaroxaban is also already approved in the European Union for the prevention of VTE following orthopaedic surgery (see page 61), and seems on track for SPAF approval in the United States in 2011. Results from a third would-be competitor, Bristol-Myers Squibb/Pfizer's oral factor Xa inhibitor apixaban, are due to be presented in August 2011 at the European Society of Cardiology meeting in Paris, France.

Another closely watched competition to introduce a pioneering oral drug — in this case, for patients with multiple sclerosis — was won by Novartis's fingolimod (Gilenya), a sphingosine 1-phosphate receptor modulator. Fingolimod was approved by the FDA in September (see next month's in-depth analysis of FDA approvals in 2010).

The push to bring a new obesity drug to market, by contrast, brought predominantly disappointment, although there is some cause for cautious optimism (see page 5). Two candidates stumbled at the hurdle of FDA

review, and then an advisory panel endorsed Orexigen Therapeutics/Takeda's bupropion plus naltrexone combination. A decision on the anti-obesity drug is due in 2011.

Notable, expensive, flops in the clinic in 2010 (BOX 2) included Medivation/Pfizer's dimebon for moderate to severe Alzheimer's disease (AD) — which may have contributed to Pfizer's CEO Jeff Kindler's unexpected resignation — and Eli Lilly & Company's semagacestat for AD. A string of failures in AD has raised broader questions about the prevailing amyloid hypothesis of this disease, on which semagacestat was based[10].

Common interests in rare diseases

While blockbuster indications like AD remain on the radar for drug makers, companies have continued to ramp up their commitment to niche busters for rare diseases over the course of 2010 as well. Pfizer, following on from its 2009 acquisition of the rights to Protalix's taliglucerase alfa for Gaucher's disease, for example, created a small R&D unit dedicated to rare diseases[11]. Pfizer also acquired FoldRx, who focus on therapeutics for protein misfolding diseases like transthyretin amyloid polyneuropathy[12].

Regulatory and financial incentives, such as those provided by the US Orphan Drug Act of 1983 and comparable legislation in Europe enacted a decade ago, have also had a key role in increasing interest in the field. Writing in a recent commentary piece[13], Timothy Coté, Director of the US FDA's Office of the Orphan Products Development, argued that further developments, including comprehensive analysis of rare disease review and regulation, "are poised to increase the momentum of rare disease R&D". It is no surprise, then, that Pfizer is not the only big pharmaceutical company striving for a piece of the pie. Sanofi–Aventis, for instance, is engaged in a long-running bid to acquire the biotechnology company Genzyme, which has built its business model on a host of drugs for rare diseases. And following the establishment of a rare diseases unit in 2010, GlaxoSmithKline recently formed an alliance with Fondazione Telethon and Fondazione San Raffaele to develop novel gene therapy approaches for rare disorders such as adenosine deaminase-severe combined immune deficiency, Wiskott–Aldrich syndrome (WAS) and β-thalassaemia.

2011: gene therapy revival?

In addition to GlaxoSmithKline's recent deal, a cluster of clinical data in 2010 indicated that gene therapy could be on the up, after a decade of disappointments and setbacks. For example, lentiviral delivery of the β-globin gene via autologous haematopoietic stem cell transfusion proved safe and effective in one patient with severe β^{E}/β^{0}-thalassaemia[14]. Retroviral delivery of the *WAS* gene using the same strategy improved the symptoms of WAS in two patients for up to 3 years, with no treatment-related adverse events[15]. And in a larger 39-patient placebo-controlled Phase II study, presented at the 2010 American Heart Association meeting in Chicago, USA, Celladon's adeno-associated virus Mydicar (sarcoplasmic/endoplasmic reticulum calcium ATPase 2a (*SERCA2a*) gene therapy) met its primary safety and efficacy end points, including incidence of fatal and non-fatal cardiovascular events, in patients with advanced heart failure.

Although such results are encouraging, regulatory approval remains an unachieved goal. Leading the charge for change, potentially in 2011, is Amsterdam Molecular Therapeutics (AMT), who has filed Glybera (lipoprotein lipase (*LPL*) gene therapy) for the treatment of LPL deficiency in the European Union. AMT is anticipating a decision from the regulators in 2011. "It would be a landmark event to have the first gene therapy approved, for any indication," said Jean Bennett, a professor of ophthalmology who works on gene therapy at the University of Pennsylvania, USA. "I hope they can do it."

Box 2 | **Top flops**

As ever, the high attrition rate in late-stage drug development took its toll in 2010. Thomson Reuters Life Science Consulting compiled its list of the top flops of 2010, as ranked by loss of risk-adjusted consensus-analyst forecasted sales over the next 20 years (see the table). The top 10 failures — including drugs that have been discontinued and those that failed pivotal trials or face possibly surmountable regulatory setbacks — are anticipated to cost the industry nearly US$74 billion (lost revenue relates only to the indications in which the drug failed, and some of the listed drugs are still in development for other indications). Despite the hold-ups, some of these products could still make it to market. Thomson Reuters' CMR International estimates that the sunk cost of late-stage failure was approximately $300–500 million per project.

Company	Product*	Indication	Status	Lost revenue‡
Roche/ Biogen Idec	Ocrelizumab	RA/lupus	Discontinued	$13 billion
AstraZeneca	Motavizumab	RSV	CRL; another trial requested	$13 billion
Sanofi–Aventis	NV1FGF	PVD	Discontinued	$11 billion
AstraZeneca	Zibotentan	Prostate cancer	Pivotal trail failed; two more trials ongoing	$11 billion
Merck & Co	Vicriviroc	HIV	Discontinued	$10 billion
Roche/Ipsen	Taspoglutide	Type 2 diabetes	Pivotal trials halted on safety concerns	$4.8 billion
AstraZeneca	Cediranib	Cancer	Discontinued	$4.4 billion
Eli Lilly & Company	Semagacestat	Alzheimer's disease	Discontinued	$3.9 billion
Novartis/ Antisoma	ASA404	NSCLC	Discontinued	$1.8 billion
Pfizer/ Medivation	Dimebon	Moderate to severe Alzheimer's disease	Discontinued	$0.8 billion

*Drugs may still be in development for other indications. ‡Forecasted lost revenue over 20 years (US$, risk adjusted). CRL, complete response letter; NSCLC, non-small cell lung cancer; PVD, peripheral arterial disease; RA, rheumatoid arthritis; RSV, respiratory syncytial virus.

1. Challenger, Gray & Christmas. Planned Job Cuts Surge to Eight-Month High. 48,711 November Job Cuts up 28% from October. *Challenger, Gray & Christmas website* [online], http://www.challengergray.com/press/PressRelease.aspx?PressUid=151 (2010).
2. Green, G. C. The Impact of US Healthcare Reform on Pharma: Analyzing the effects. *Business Insights* 1–82 (2010).
3. Mullard, A. *Nature Rev. Drug Discov.* **9**, 905–906 (2010).
4. Jones, D. *Nature Rev. Drug Discov.* **9**, 345–348 (2010).
5. [No author listed]. *Nature Rev. Drug Discov.* **9**, 423 (2010).
6. Kwak, E. L. *et al. N. Engl. J. Med.* **18**, 1693–1703 (2010).
7. Opar, A. *Nature Rev. Drug Discov.* **9**, 501–503 (2010).
8. Hughes, B. *Nature Rev. Drug Discov.* **9**, 903–906 (2010).
9. Connolly, S. J. *et al. N. Engl. J. Med.* **361**, 139–1151 (2009).
10. Extance, A. *Nature Rev. Drug Discov.* **9**, 749–751 (2010).
11. Shaffer, C. *Nature Biotech.* **28**, 881–882 (2010).
12. Jones, D. *Nature Rev. Drug Discov.* **9**, 825–827 (2010).
13. Coté, T. R. *et al. Nature Rev. Drug Discov.* **9**, 901–902 (2010).
14. Cavazzana-Calvo, M. *et al. Nature* **467**, 318–322 (2010).
15. Boztug, K. *et al. N. Engl. J. Med.* **363**, 1918–1927 (2010).
16. Dawkes, A. & Papp, T. *Nature Rev. Drug Discov.* **9**, 909 (2010).