Recent FDA approvals provide reason for cheer

Amidst cries that the pharma industry is in perpetual decline and with widespread investor disillusionment with the biotech sector, we review some key FDA approvals of 2011 and find grounds for optimism.

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About the author

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Both biotech and pharma investors are in despair. KPMG recently concluded that returns on R&D investment among the 30 leading drug companies fell by 50% since 1990. At a 10% rate of return last year, they claim that pharma R&D is barely adequate to cover the cost of capital.

Moreover, a September report from Deutsche Bank that found the seven largest European drug makers spent $161bn in R&D during 2007-11 to produce drugs with a net present value of just $86bn.

Whilst R&D is destroying value faster than Lehman's CDOs, FDA has had a stellar year, approving 34 new molecular entities. That number tops all other performances of the past decade, with the exception of 2007 (37 approvals). For pharma bosses contemplating ritual disembowelment, there are signs of salvation. We examine some of the approvals in 2011 and find room for optimism - especially for those prepared to embrace risk and innovation.

Cancer Immunotherapy – a new dawn

The concept of harnessing the power and exquisite selectivity of the immune system to fight cancer is a holy grail of medical research. In the summer of 2009, Bristol Myers Squibb (BMS) bought Medarex for $2.4bn. The transaction gave BMS a ticket to the antibody game with Medarex's UltiMab platform, as well as rights to seven antibodies in development. One of those was Yervoy (ipilimumab), a human mAb that blocks CTLA4, a modulator of T-cell activity. By blocking CTLA4, the brakes on the immune system are released and the power of T-cell killing is unleashed onto tumour cells.

Whilst Pfizer canned its competing anti-CTLA4 program after a negative Phase III (and since sold it to AstraZeneca), BMS continued with an innovative clinical program, persuading FDA to reconsider the definition of a response rate and eventually demonstrating compelling evidence of efficacy in metastatic melanoma, an area of severe unmet medical need. 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[1].

Even when priced aggressively ($120k per patient) and with 13% of patients experiencing severe or fatal autoimmune reactions, Yervoy is selling strongly, chalking up quarterly sales of $95 million – an exceptional launch. This contrasts with the experience of Dendreon's Provenge, a patient-specific cancer vaccine approved a year before which has (predictably) disappointed commercially.

The Provenge and Yervoy approvals mark a major advance in cancer immunotherapy. But despite Yervoy's toxicity limitations, it heralds a new dawn in cancer therapy by knocking out a powerful tumour defence mechanism and thus enabling other immunotherapy approaches. The National Cancer Institute were quick off the mark, recently publishing a combination of Yervoy and Prostvac (a prostate cancer vaccine owned by Bavarian Nordic) in a Phase I trial, with 14 advanced prostate cancer patients experiencing PSA declines, six of which were greater than 50%[2]. If it reaches the market, the combination will be inaccessibly expensive, but the price of Yervoy will decrease over time in the face of biosimilar and biobetter competition.

Over the next year or so, GSK's MAGE-A3 cancer vaccine, subject of the world's largest lung cancer clinical trial will report. In a Phase IIb it reduced the risk of relapse by 27% and, in the words of Andrew Witty, the Phase III results announcement could be "sphincter tightening".

Antibody Conjugates – here to stay

The concept of harnessing the specificity of antibodies to deliver a toxic payload to tumours is simple to grasp but herculean to execute. After a series of setbacks for other immunoconjugates, the field received a boost with the August approval of Adcetris, developed and marketed by Seattle Genetics (SGEN) for two niche lymphomas. The drug represents the only approved antibody conjugate following the voluntary withdrawal of Mylotarg by Pfizer in 2010. The challenge of ensuring the toxin dropped off at the right time, in the right place, is significant.

It seems SGEN may have cracked it. The chimeric human-mouse mAb conjugated to auristatin, a microtubule disrupting agent, targets the SC30 receptor on the surface of lymphoma cells. After binding to CD30, the antibody is internalised along with the toxin.

A high response rate in two single arm studies (73% in one, 83% in the other), led to a unanimous decision by the FDA's Oncologic Drugs Advisory Committee for approval, leading to accelerated approval on the basis of non-randomised data. Note, it doesn't cost everyone $1bn to develop a new drug.

Watch out for more news of antibody conjugates delivering commercial and clinical value, including the expansion of Adcetris' label in other haematologic malignancies and Roche's T-DM1, which has been filed with the FDA for the treatment of HER-2 breast cancer.

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[1] Robert, C. *N. Engl. J. Med.* (2011)

[2] Madan, RA *Lancet Oncology* (2012)

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New Hammers for Old Nuts

The last drug to be approved for systemic lupus erythematosus was Plaquenil (Sanofi-Aventis), which gained approval in 1955 for lupus and malaria. It was with some exhilaration therefore, that Benlysta, manufactured by Human Genome Sciences and partnered with GSK, was approved in March 2011. The development of belimumab combined a pioneering approach to genomics-based gene discovery, a disciplined clinical strategy and a willingness to take calculated risks (reviewed in Nature Biotechnology[3]).

The drug is a human mAb that binds and neutralizes B-lymphocyte stimulator (BLyS). The milestone is all the more remarkable in that as recently as 1998, BLyS was itself an unknown entity to the scientific community. By coupling advances in automated DNA sequencing and a vision for genomics-based drug discovery, HGS pioneered the development of this new therapy.

Unfortunately, the drug has underperformed to date, with questions about marketability and clinical practice.

Companion Diagnostics – delivering value

Despite the sceptics ("in 10 years, we'll be saying stratified medicine is about 10 years away"), companion diagnostics are already reducing development costs and allowing new medicines to be targeted to groups of patients where they'll work. Recent approvals include Zelboraf (vemurabenib) from Genentech and Xalkori (crizotinib) from Pfizer.

Zelboraf targets mutated BRAF protein, which disrupts cell regulation and promotes tumour growth. At ASCO 2011, investigators presented six month survival of 84% survival versus 64% for patients with metastatic melanoma. Zelboraf was approved alongside a multiplex PCR-based diagnostic for the *BRAF* V600E gene.

Pfizer's Xalkori was approved with a fluorescent *in situ* hybridisation test for detecting rearrangements of the anaplastic lymphoma kinase (*ALK*) gene for non-small cell lung cancer patients.

There are several targeted therapies in the late stage pipeline, each one chipping away at the death sentence that is metastatic cancer.

Rapid Development – embracing new technology

If pharma R&D productivity is a function of costs and revenues, then strategies to reduce development timelines (reducing cost and generating revenues early) are paramount.

"There are several targeted therapies in the late stage pipeline, each one chipping away at the death sentence that is metastatic cancer"

[3] Stohl W. *Nature Biotechnology* (2012)

So there were several reasons to celebrate on November 16 when FDA approved Jakafi (ruxolitinib), a small-molecule drug against myelofibrosis and other myeloproliferative disorders from Incyte and Novartis.

Not only is Jakafi the first treatment approved against myelofibrosis and similar neoplasms, the development program also exemplifies a rapid development time—six years after an activating mutation in JAK2 was first identified in this cancer.

Incyte's embrace of patient-reported outcome tools in the trial design was key in facilitating full approval[4]. One of the two registration trials included a secondary end point based on a patient-reported outcome: the proportion of patients with a 50% or greater reduction in score of a total of six symptoms from baseline to week 24. This was measured using a novel instrument, the modified myelofibrosis symptom assessment form (MFSAF) v2.0 diary, which Incyte developed in consultation with patients and FDA during early phase I/II testing. The MFSAF is an electronic, handheld device that included a daily alarm reminding patients to log in and record their symptom scores, which were transmitted to a database on a daily basis. Tracking of all the symptoms by MFSAF enabled full approval.

Outlook

It's invigorating to see many companies receive their first approvals, especially with first in class programs. For a biotech, a first in class molecule can be somewhat of a curse, requiring significant data and therefore cash to convince the world of the program's value. It is imperative that cash continues to flow to these companies and programs, the return on investment can be substantial. We will continue to see pioneering programs reaching the market and, if they address real unmet needs, securing payor approval and delivering substantial returns.

The market success of Genzyme's Cerezyme 10-15 years ago sparked interest in orphan drugs and the industry is now enjoying record numbers of approvals for these indications. These should continue for the foreseeable future.

Investors, take heart!

[4] Moran N *Nature Biotechnology* (2012)

About Alacrita

Alacrita provides expertise-based consulting services to the pharmaceutical, biotechnology and life science sectors.

We combine extensive industry experience and broad functional capabilities to help our clients create sustainable value, providing:

- multidisciplinary project teams to conduct specific assignments
- instant expertise: high-level strategic, commercial and technical
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Alacrita's team has industry experience and a consulting track record, ensuring that projects are delivered with both professionalism and real-world relevance.

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