Evaluate Vantage

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Big pharma's key events for the next six months

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The outcome of the dapagliflozin's date with the FDA was widely expected to end with rejection and today it came to pass. As one of the most notable potential product approvals of the first half of 2012, a request for what are likely to be pretty extensive further trials is a disappointing result for partners AstraZeneca and Bristol-Myers Squibb.

There are plenty of other big decisions on the horizon for the world's biggest drug makers. An analysis of what these companies have in store in the first six months of the year reveals Astra still has some big patent challenges pending and Bristol-Myers will hear whether its biggest growth driver, Eliquis, passes FDA muster. Other regulatory milestones include a US review of Amgen's Xgeva in preventing prostate cancer spreading to the bone, the EU's verdict on Novo Nordisk's new insulin degludec and possibly the first interim analysis from a large outcome study being conducted by Roche with dalcetrapib, a high risk product that carries huge potential (see tables below.)

Life is rarely quiet for companies the size of Pfizer and GlaxoSmithKline. In an attempt to focus on the biggest milestones these groups are facing, the following notable events have been extracted from EvaluatePharma's Calendar of Events; an analysis of what is on the horizon for smaller companies in the next six months will follow.

Back to court

Patent decisions					Annual Sales WW ($m)				
Product	**Pharmacological Class**	**Company**	**Event**	**Date**	**2012**	**2016**	**Product NPV ($bn)**	**NPV as % of Market Cap**	**Mar Ca ($b**
Crestor	Statin/ HMG CoA reductase inhibitor	AstraZeneca	Court decision on appeal	H1	6,648	5,370	11.2	18%	62
Copaxone	MS agent	Teva Pharmaceutical Industries	Patent update	H1	4,101	2,392	7.6	18%	42
Seroquel XR	5-HT2 (serotonin) & dopamine D2 antagonist	AstraZeneca	Patent trial decision	H1	3,536	1,651	5.4	9%	62
Lovaza	Omega-3 fatty acid	GlaxoSmithKline	Patent update	H1	922	436	0.7	1%	11

AstraZeneca has a couple of legal cases hanging over Crestor and Seroquel XR that are widely expected to go its way. Anything other than complete victory will be a disaster for the company that is struggling to bring though new products to replace these two huge earners, as they approach the end of their patented lives.

The Anglo-Nordic group won the first big case around Crestor in mid 2010, with a judge ruling the patent that protects the statin out to 2016 is valid and enforceable, non-obvious and was properly re-issued (*Astra wins crucial Crestor battle but efficacy debate will continue, June 30, 2010*). The handful of generic firms that lost that case appealed, and that case went to the higher courts at the beginning of October last year. The decision was expected to take three to six months meaning the outcome should be known in the next couple of months.

In terms of Seroquel, Astra won a case back in 2008 protecting the patent around the original instant release molecule (*Two down, one to go in Astra's key patent battles, July 2, 2008*). That expires in March this year and the generic industry's attention has turned to the extended release formulation, which the company contends is protected until November 2017.

Astra settled with first-to-file Handa Pharmaceuticals in September last year, which agreed to hold off launch until November 2016, and two other firms a few days later on the same terms. But a number of other generic challengers have assumedly decided to continue to test the strength of the patent through the courts.

Assuming they refuse to settle a decision from the court could well be handed down around the time the patent on the original molecule expires. If it goes against Astra, the whole Seroquel franchise will crumble that day.

Analysts reckon the IR tablet accounted for almost three-quarter of Seroquel's $5.7bn sales last year, after a push by Astra to switch patients onto the XR tablet. By 2016 that picture is predicted to switch around with the XR tablet accounting for three-quarters of the $1.7bn sales forecast for that year.

Other important legal spats on the horizon include the ongoing Lovaza case with Teva and Par Pharmaceuticals, an outcome that is relatively more important for Glaxo's partner Pronova (*Pronova's compromise with Apotex a step in the right direction, March 30, 2011*). A outcome is due anytime and some believe the remaining contenders will be less likely to roll over.

Finally Teva is unlikely to be enjoying its time on the other side of the courtroom, defending itself against challenges from two generics franchises: Momenta Pharmaceuticals/Sandoz and Mylan/Natco Pharma (*Event – Teva needs Copaxone patent victory, August 22, 2011*).

The drug's patents expire in May 2014 but the 30-month stay against Momenta and Sandoz's challenge expired in March last year. As such, losing the patent litigation and subsequent FDA approval for one or both generic versions could potentially see Copaxone under threat much sooner. The trial started in September and the outcome is arguably the biggest event on the horizon for the Israeli generics firm.

Regulatory dates

By far the most valuable drug in this part of the analysis and one that could continue the revival in Amgen's fortunes is bone cancer drug Xgeva. The monoclonal antibody is up for US approval by April 26 in prevention of bone metastases, but before that it has to get past an FDA panel at the beginning of next month (*Event - Survival the question in Xgeva bone metastases panel, January 17, 2012*).

Forecast to be the biggest growth driver at Amgen over the next five years Xgeva is worth a whopping $10.7bn to the company, or 20% of its share price. But that sum encompasses all indications for Xgeva including prevention of fracture in patients with bone metastases, where is it already approved and expected to see the majority of its $2.5bn sales in 2016.

However, many are expecting the drug to struggle to win backing in the bone metastases prevention setting as it failed to show a survival benefit, while the 4.3 month delay in worsening of symptoms may not be enough to convince regulators approval is warranted.

Regulatory decisions					Annual Sales WW ($m)				
Product	**Pharmacological Class**	**Company**	**Event**	**Date**	**2012**	**2016**	**Product NPV ($bn)**	**NPV as % of Market Cap**	**I**
Xgeva	Anti-RANKL MAb	Amgen	AdCom/PDUFA	Feb 8/Apr 26	862	2,522	10.7	20%	
Eliquis	Factor Xa inhibitor	Bristol-Myers Squibb	PDUFA	Mar 28	284	3,514	7.0	12%	
Eliquis	Factor Xa inhibitor	Pfizer			-	-	5.4	3%	
Tofacitinib	Janus kinase-3 (JAK-3) inhibitor	Pfizer	EMA decision date	Q2	68	1,430	4.6	3%	
DegludecPlus	Insulin	Novo Nordisk	EMA decision date	Q2	27	761	2.9	5%	
Degludec	Insulin	Novo Nordisk	EMA decision date	Q2	31	676	2.5	4%	
Nesina	Dipeptidyl peptidase IV (DPP-IV) inhibitor	Takeda	PDUFA	Apr 25	456	1,303	2.3	7%	
Liovel	Dipeptidyl peptidase IV (DPP-IV) inhibitor & PPAR gamma agonist	Takeda	PDUFA	Apr 25	193	774	1.6	5%	

What those in the haematology and cardiology space will be looking for is both the US and European approval of blood thinner Eliquis for stroke prevention in atrial fibrillation. Although it will be the third to market in this area, the drug's strong clinical package make it a serious challenger to the now not-so-new kids on the block, Xarelto and Pradaxa (*Strong Eliquis result to repaint picture of blood thinner market, June 23, 2011*).

Analysts are predicting sales of $3.5bn by 2016 for the product, which is already on the market in Europe for prevention of clotting following orthopaedic surgery, so it comes as no surprise that it is BMS's biggest growth driver with an net present value of $7bn, or a chunky 12% of the US group's share price. Partner Pfizer is also set to benefit from Eliquis' future success, forecast to bank $2.13bn in alliance revenue by 2016. As such the US approval date by March 28 will be a closely watched event.

Diabetes bonanza

While March is key for BMS and Pfizer, Takeda will be looking to April for what will be a tipping point for diabetes drugs, Nesina and Liovel, in the US.

Nesina, generically known as alogliptin, has already had one bruising brush with the regulator, having received a complete response letter back in June 2009 (*Alogliptin disappointment continues for Takeda, June 29, 2009*). As such there are still risks to approval this time round, even if Takeda is armed with new cardiovascular safety data. Failure by Nesina would also drag down Liovel, which is a fixed dose combination of Nesina and the group's aging blockbuster Actos, which also has its own issues (*Takeda's Actos looks set to fade faster, June 16, 2011*).

With combined forecast sales of $1.44bn by 2016, Novo Nordisk's degludec and degludec plus are looking for European approval in April and US marketing authorisation in July. Following the failure of its other insulin drug, Levemir, to topple insulin king Lantus, the Danish group is hoping for better things with these two long-acting drugs, which could also help it stave off generic competition.

For Pfizer its big first-half event is European approval of rheumatoid arthritis drug tofacitinib, a JAK-3 inhibitor.

Pfizer has been cagey about what specific RA population tofacitinib will be used in, so if it does get European approval, it should make it clearer about the group's US intentions. Observers should expect an advisory committee hearing in the first half of the year ahead of an August PDUFA (*ACR - Pfizer's tofacitinib heads to FDA as role in RA debated, November 8, 2011*) .

Data read outs					**Annual Sales WW ($m)**				
Product	**Pharmacological Class**	**Company**	**Event**	**Date**	**2012**	**2016**	**Product NPV ($bn)**	**NPV as % of Market Cap**	**Mark Ca ($b**
RG1658 (JTT-705)	CETP modulator	Roche	Phase III interim analysis	H1	-	597	1.5	1%	158
Riociguat	Guanylate cyclase activator	Bayer	Phase III results	Mid 2012	11	426	1.1	2%	61.
Solanezumab	Anti-beta amyloid MAb	Eli Lilly	Phase III results	H1	-	299	1.0	2%	46.
TC-5214	Alpha 4 & beta 2 nicotinic agonist	AstraZeneca	Phase III results	H1	-	224	0.5	1%	62.

The first half of the year should yield the first signals from the closely watched phase III trial of Eli Lilly's Alzheimer's drug solanezumab. Analysts believe the results of an interim futility analysis could emerge when the company announces annual results on January 31. Full results from the two studies, called Expedition and Expedition2, are not likely to emerge until later in the year.

When the second pivotal phase III trial of the depression drug TC-5214 failed to meet the primary endpoint back in December, AstraZeneca and partner Targacept faced a dismal Christmas. The new year headache could continue with top line results for both the fixed dose trials and long term study expected in the first half of 2012, with low expectations that the remaining trials will demonstrate positive outcomes (*Pipeline setbacks hurt AstraZeneca, December 20, 2011*).

As the development frontrunner of CETP inhibitors, Roche is set to report an interim analysis of 70% of events in the ongoing pivotal study of dalcetrapib (RG1658) in the next few months. With the failure of Pfizer's torcetrapib due to increased risk of cardiovascular events, the interim analysis of dalcetrapib could provide important information on the drug class and the potential of Merck's anacetrapib, a more potent CETP inhibitor with results due in 2017.

Final data from the dalcetrapib study are not expected until 2013.

With accelerated trial recruitment, results from a phase III results of Bayer's pulmonary hypertension (PAH) drug Riociguat could be available mid 2012, at least six months earlier than expected, according to analysts at JP Morgan.

Currently Riociguat is also in phase III trials for chronic thromboembolic pulmonary hypertension, for which surgery is currently the only option. In phase II trials Riociguat was well tolerated with a good safety profile; with the potential to address an unmet medical need analysts at Morgan Stanley reckon the drug could reach blockbuster status.

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