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Triple-negative salvage for Eisai's down-not-out eribulin?

Encouraged by promising signs of activity, particularly in certain patient subsets, in the earlier line treatment of advanced breast cancer, Eisai is stressing that it remains committed to developing its novel microtubule dynamics inhibitor Halaven (eribulin mesylate) in this setting.

But additional studies will be needed to better elucidate the drug's benefits as part of a more focused strategy following the overall negative results from the comparative Study 301. While no decisions have been made, new data from the program suggest that the triple-negative form of breast cancer (disease negative for human epidermal growth factor receptor 2 (HER2), estrogen and progesterone receptors) may emerge as the lead target.

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'Ignore our drug prices', Greece tells Europe

National pricing and reimbursement authorities in Europe should not use Greek medicine prices to set their own prices, the Greek health ministry has said on its website.

"The current Greek pricing system is based on the exceptional and harsh economic, social and medical factors that are specific to Greece. The Greek ministry of health asks competent authorities in other countries not to refer to those prices in their national pricing and reimbursement decision-making process," says the announcement.

Companies will be hoping that national authorities take note. Drastic price cuts in Greece have been a concern for industry for some time, not only because of the losses in Greece, but also because several countries determine their own medicine prices by directly or indirectly referencing prices in Greece (as well as other markets). Both EFPIA and EUCOPE, which represent pharmaceutical companies in Europe, have complained that wealthier countries are referencing prices in lower-income countries, including Greece. For example, Germany now uses Greek prices in the procedure for fixing drug prices if negotiations between health insurers and companies fail following the early benefit assessment.

Firms are taking a hit. In 2011, a 10% price cut in Greece lost firms €299 million there and €799 million in European countries that reference Greece in some way, according to Global Insights. The global impact was €2.15 billion (scripintelligence.com, 2 March 2012).

Industry claims that price referencing erodes differential pricing in Europe and makes it hard for companies to affordable prices in lower-income markets.

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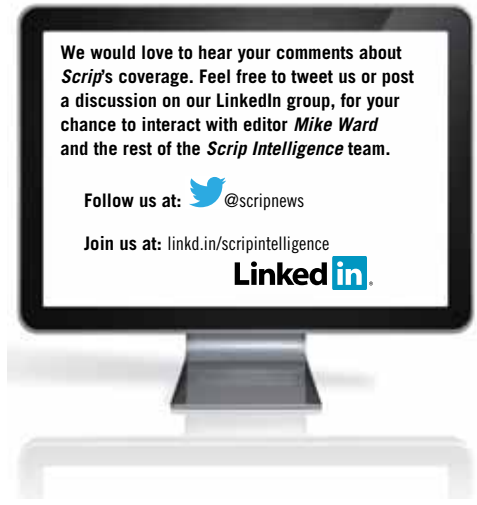

Mike Ward,
Editor,
Scrip Intelligence

In the much loved wintry tale written by AA Milne, Pooh, a bear of very little brain, sets off in the snow for an Expedition to the North Pole.

On the way, he meets his friend Piglet. Both trudge together through the thickening snowfall, singing songs to steel themselves against the cold and other dangers of the wood.

After a while, they come across the tracks of a large, heavy and ferocious beast, the Woozle. And the Woozle tracks are then joined by those of a smaller but potentially equally ferocious animal, the Wizzle.

A little further on, still more tracks suggest that the original Woozle and Wizzle have been joined not only by another Woozle, but also by another Wizzle.

Pooh and Piglet are entirely fictional. They are also wholly delusional. The tracks of the Woozle and the Wizzle are Pooh and Piglet's own footprints. Robbed of landmarks, the pair have simply gone round in circles in the snow.

In Eli Lilly's case, the destination of its EXPEDITION was not the North Pole but the mystifying and barren landscape of Alzheimer's disease. EXPEDITION is the series of clinical studies Lilly used to look at whether and how the anti-amyloid antibody solanezumab might slow Alzheimer's progression.

In its original study, results of which were reported in August 2012, it was clear that the drug had no discernable impact on patients with severe Alzheimer's disease. But there were signs of efficacy in patients with mild-to-moderate disease. The drug slowed the rate of loss of cognitive function. On the basis of those original data alone, Lilly might have been able to file for approval for an indication in mild-to-moderate disease.

But in the event, after discussions with the US FDA, the company has decided to circle around and undertake another round of EXPEDITION, this time looking at mildly-affected patients.

This may provide stronger data for an earlier preventative indication for sola. What it certainly does do is set back solanezumab's approval date (and revenue-generation) at least four years.

Lilly has to hope that the milder Wezzle is a real monster.

'Bad pharma' gets a scolding from Goldacre

SCOLDACRE: Industry critic tells pharma that full transparency is in industry's best interests

Criticizing the pharmaceutical industry, I've recently discovered, is a little like questioning a cult: there are outlandish smears, lurid denunciations, and implausible outright denials. People within the community award themselves a point for this behavior, while outsiders look on in amazement. I'd like to speak with those of you who are able to step outside of this game.

Firstly, while everyone is entitled to their own opinions, we all have to work with the same facts. The problem of missing data is real, and ongoing. The best current evidence shows that around half of all trials are never published, in industry and in academia. Industry's first response is always: "this has been fixed". But all these supposed fixes have been incomplete by design, and failed in practise.

The best published evidence shows that ICMJE rules on registering trials before they begin have been widely ignored, years after they were supposedly implemented. Research in the *BMJ* from 2012 shows that the laws on posting trial results at clinicaltrials.gov within one year have been ignored by four out of five trials, and it's now four years since those rules were passed. Even if these rules had been enforced, they still don't get access to trials conducted before 2009.

Doctors cannot practice evidence-based medicine if half the information from before 2009 is still missing, and much of it is withheld on direct request. But this is what happens, and quite legally. Roche, for example, are still refusing to hand over Clinical Study Reports on Tamiflu to the independent academics at the Cochrane Collaboration. And yet this information is vitally important, because we are increasingly seeing that brief academic journal articles can give a very misleading picture about what actually happened in a study. Finally, despite several well-received promises for the future, so far almost no company has ever shared one single file of individual patient data from a clinical trial.

If this was all news to you, I hope you now accept that important information on clinical trials continues to be withheld from doctors and patients.

There are plenty of swivel-eyed quacks and conspiracy theorists out there, who hate everything we both stand for (especially you). But people like me only care about bad behavior in industry for one reason: we want evidence-based medicine to be as good as it can be. This means good quality trials – fair tests – conducted as frequently and efficiently as possible, with all the results reported, and accurate summaries of all the evidence put into practice.

Where industry has resisted this – against its own interests, in my view – we need to understand why. I don't think you are bad people. Much of what pharma does is good, of course, but for all of us in medicine this is both a blessing and a curse. For example: bad trials, missing data, and biased dissemination of evidence through marketing, might all mislead doctors into wrongly believing that a new drug is better than an older, cheaper one. Any drug that is wrongly believed to be the best, when it's actually only mediocre, harms patients, because it deprives them of better treatments. But even a second rate drug does patients some good, undeniably. And so perhaps we all allow ourselves to become too relaxed about these problems.

But bad practices have also persisted through lack of vision. When unflattering trial data are glossed over, an individual company can be rewarded with higher sales. This short-term gain comes at the expense of everyone's collective reputation: and it is amazing, since you save lives, that your reputation is so poor. If you advocated strongly for more transparency, for you and your competitors, universally and internationally, in law, then all companies would compete on an equal footing, ethically and transparently.

This will come to your industry, whether you like it or not. Transparency is an unstoppable tide, throughout society, as we enter the era of big data, and it's not always comfortable. The US and UK governments now release terabytes, knowing some of it may embarrass them, but also knowing that "many eyes" can find patterns – and spot problems – better than a few, behind closed doors.

In the worst scenario, for you, we will all get a sharper sense of what works and what doesn't. Success will be rewarded more; second-best drugs, less so. This sharpening of rewards might be uncomfortable, and it might accelerate innovation. But it will come, and I'll happily help you to stop fighting it.

http://bit.ly/Z3DkRN

Ben Goldacre

Ben Goldacre is a doctor and the author of Bad Pharma, he can be contacted at ben@badscience.net.

Triple-negative salvage for Eisai's down-not-out eribulin? (Continued from page 1)

NO DECISIONS YET: Eisai and investigators are still digesting the full 301 results

From top-line results released in July (scripintelligence.com, 10 July 2012), it was already known that eribulin missed pre-defined criteria for statistical significance against the co-primary endpoints of overall survival (OS) and progression-free survival (PFS) in the 301 trial, the first to compare it with Roche's Xeloda (capecitabine) for locally advanced or metastatic breast cancer.

Perhaps for this reason, and the hope of targeted use in the earlier setting, investors appeared sanguine about the new results, presented at the CTRC-American Association for Cancer Research San Antonio Breast Cancer Symposium in Texas late last week. Eisai's shares closed up by 0.14% at ¥3,505 ($42.64) in Tokyo on 10 December, the first full trading day after the additional findings were announced.

Analyst Ryoichi Urushihara at Nomura Japan Equity Research said that, given triple-negative patients account for 15-25% of the breast cancer total and have no effective treatments, eribulin might be an option in the future. "We think Halaven could become an essential treatment for patients with hard-to-treat [breast] cancer, though further trials will be needed before approval," he said in a research note.

Past failures of novel therapies for triple-negative disease have included Sanofi's PARP inhibitor iniparib in early 2011, while more recently Roche's Avastin (bevacizumab) missed its primary endpoint in the Phase III BEATRICE trial (scripintelligence.com, 17 October 2012).

The 301 trial assessed eribulin monotherapy in women who had failed up to three chemotherapy regimens (no more than two for advanced and/or metastatic disease) including a taxane and an anthracycline, either in the (neo)adjuvant setting or for locally advanced or metastatic disease.

The majority of patients received eribulin as a first- (27.2%) or second-line (57.4%) chemotherapeutic regimen for metastatic disease.

The new data from the 1,102-patient study show that the median OS for eribulin was 15.9 months, compared with 14.5 months for capecitabine (HR 0.879; 95% CI: 0.770-1.003; p=0.056). Median PFS was 4.1 months versus 4.2 months respectively (HR 1.079; 95% CI: 0.932-1.250; p=0.305).

However, there was a (non-significant) trend towards improved comparative OS for eribulin in the intent-to-treat population, and an early improvement in one-, two- and three-year OS rates for the Eisai drug was maintained throughout the study. These figures were 64.4% for eribulin and 58% for capecitabine at one year (p=0.0351), 32.8% vs 29.8% at two years (p=0.3235) and 17.8% vs 14.5% at three years (p=0.1751).

Eisai and investigators are still digesting the full 301 results and there have been no decisions yet on the type and timing of any additional clinical work or sharpened target indication for the drug, which is currently approved in around 40 countries only as a third-line therapy for metastatic breast cancer in patients whose prior therapy should have included an anthracycline and a taxane.

Investigators are also still compiling 301 data for a quality of life analysis, which they said would help guide decisions on further studies.

Approval for earlier line use is seen as not only providing another clinical option but is also significant for expanding sales of eribulin, which at an Eisai-projected ¥28.5 billion ($347 million) for the fiscal year to 31 March remain modest.

subset results

Eisai noted that the 301 study - which first opened for recruitment in 2006 - included HER2-positive patients, which would not now usually be enrolled in such a trial given the emergence of targeted therapies for those with the mutation.

Excluding these, an exploratory analysis of the 755-patient HER2-negative subset (a pre-specified stratification factor in the study protocol) showed that median OS for eribulin remained at 15.9 months, but fell to 13.5 months for capecitabine (HR 0.838; 95% CI: 0.715-0.983; nominal p=0.030), widening the gap between the drugs.

In HER2-positive patients only (169 in Study 301), median OS was 14.3 months versus 17.1 months (HR; 95% 0.965; CI: 0.688-1.355), suggesting that the inclusion of these patients "dragged down" the overall study results.

"The results suggest that there is a possible clinical advantage over capecitabine in certain patient populations that warrants further analysis to fully understand the implications of this study in clinical practice," said co-primary investigator Dr Christopher Twelves, professor of clinical cancer pharmacology and oncology at the University of Leeds and St James' University Hospital in the UK.

And while the overall study missed its endpoints, "numerically, the overall survival with eribulin was better than with capecitabine," Dr Peter Kaufman, associate professor of medicine at the Geisel School of Medicine and the Norris Cotton Cancer Center in the US and another of the investigators, told the San Antonio meeting.

But it was in the 284 triple-negative breast cancer patients in the study that eribulin appeared to hold most promise. Median OS for eribulin here was 14.4 months, five months longer than the 9.4 months for capecitabine (HR 0.702; 95% CI: 0.545-0.906; nominal p=0.006).

In other subgroup analyses, eribulin also showed median OS better than capecitabine in both estrogen receptor-positive (18.2 vs 16.8 months) and -negative (14.4 vs 10.5 months) patients.

The other comparative data from San Antonio being watched closely related to major side-effects (at least a 20% incidence of all grades), and the picture here was more mixed. Rates of neutropenia (54.2% for eribulin versus 15.9% for capecitabine), leukopenia (31.4% vs 10.4%) and alopecia (34.6% vs 4.0%) were all higher for the Eisai drug, while eribulin came out better for hand-foot syndrome (0.2% vs 45.1%) and diarrhea (14.3% vs 28.8%), and was similar to capecitabine for nausea (22.2% vs 24.4%).

The clear take-away message from investigators and the company was that eribulin may have failed in the 301 study, but still holds promise for earlier use in selected breast cancer patients.

Dr Kaufman stressed that 301 was the first study showing activity for eribulin in the earlier line therapy of metastatic breast cancer, and that "overall, it has potentially comparable activity to capecitabine, which is a widely used treatment in this patient population."

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HTA bodies likely to block European pricing directive

National regulators in Europe and industry organizations find themselves united in opposing the European Directive on pharmaceutical pricing and reimbursement, but for quite different reasons. The measure is due before the European Parliament's ENVI committee (Environment, Public Health and Food Safety) 18 December. Industry dislikes the current form of the directive because it threatens differential drug pricing in Europe. The national regulators dislike it because it restricts the amount of time that member states are allowed in order to reach decisions on pricing and reimbursement.

The EU's Council of Ministers, which represents member states, met on 7 December to discuss the directive. Germany in particular seems opposed to the directive and seems set to oppose it at the Council of Ministers, the final sign-off phase for national politicians. According to a source close to the German government, the commission's proposal is "undiscussable". The source said that other member states are unhappy, too.

The directive reduces the time for pricing and reimbursement decisions from 180 to 120 days, unless a complex health technology appraisal process is involved when the timeline will remain at 180 days.

The commission also proposed that these timelines be enforced. National authorities would set up a 'designate body' with the power to act when timelines have been exceeded by awarding damages to applicants or imposing penalty payments calculated according to the number of days of delay. Industry has long commented that the main problem with the directive was a lack of enforcement.

There is still time for the directive to be tweaked before it approaches the council. After examination by ENVI, the directive will go to a full sitting of the European Parliament. Only then will it go to the Council of Ministers.

"Some big member states are worried about the timelines and enforcement measures," said Dr Alexander Natz, secretary general of EUCOPE, which is taking part in discussions on the directive. However, he was unable to comment on which member states were putting up a fight.

Germany has a particular problem with this schedule because its 2011 AMNOG healthcare reform law outlines a pricing process taking 15 months or more. Pricing decisions elsewhere in Europe also take much longer than 180 days: in Italy, the mean is 326 days, in Spain and Portugal 349 days, and in Belgium 392 days, according to data from Assobiotec, the Italian biotech association.

The iterative German process is lengthier still: companies suggest a price, then, a benefit assessment comparing the price and performance of a drug against predefined competitors is used to inform price negotiations between companies and health insurers. If there is no agreement, the matter can go to arbitration.

The German health ministry declined to comment on the directive other than to say that Germany wanted "maximum transparency and that the legislation offers maximum transparency for manufacturers, patients and physicians".

Concern about the directive does not stop with member states. EUCOPE has fought against a number of parliamentary amendments that would make the true price of the drug, including rebates and discounts, available to pharmacists and physicians, thereby putting them in the public domain. Although some amendments to this effect have been withdrawn, several others remain.

Exposing real prices is problematic for companies given the rise of reference pricing in Europe and makes differential pricing very difficult. "There is no evidence that price transparency brings down prices ... companies are willing to contribute to local market realities by offering discounts, but if you re-import them, it becomes a problem," said Dr Natz. Increasingly converging prices actually make drugs more expensive for countries in less wealthy member states, he said.

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Teva CEO aims to reshape 111-year-old firm

Teva's newly anointed president and CEO Dr Jeremy Levin, who took the reins of the company in May, wants his 111-year-old firm to be known as more than the generic drug king with one major patented medicine – Copaxone (glatiramer acetate) – and has decided to reach for the stars in reshaping the Israeli manufacturer.

Indeed, as part of Teva's pursuit to be the "most indispensable medicines company in the world", the firm is using a new business approach under Dr Levin's direction of assembling "constellations" of transactions, with British Columbia-based Xenon's experimental pain disorder compound XEN402 the new star.

Teva is paying the small British Columbia biotech $41 million upfront, with an additional $335 million in development, regulatory, and sales-based milestones, plus royalties on sales of the compound, which is aimed at treating pain locally at its source through blocking Nav1.7 and Nav1.8 sodium channels.

Data have demonstrated the investigational treatment is effective in relieving the pain associated with erythromelalgia, a rare neuropathic condition, Teva said.

"Every transaction must be linked to another," Dr Levin said in explaining his constellation concept on 11 December during the company's investor day. "Every time you see us do a transaction, understand that that's just the beginning – the opening stroke of another one. We are going to paint a picture, we are going to create constellations of transactions. When one transaction is done, you may not understand why it was done, but another one's coming."

Xenon's XEN402 is joining Huntexil (pridopidine), a Huntington's disease compound the Israeli drug maker acquired in September for $26 million from Danish firm NeuroSearch, in Teva's first constellation, which will focus on central nervous system (CNS) drugs, Dr Levin said, using a graphic of the 'Big Dipper' to analogize the company's new strategy, which generated a few chuckles from the audience.

Teva plans other constellations of transactions for medicines focusing on respiratory and women's health, among others, Dr Levin said.

He said the constellation idea fits with Teva's new frontier of focusing on medicines for "select medical needs" under its plan to reshape the company in a changing industry environment, where there are fewer large generic opportunities, increasing competition in commodity generics, health care systems under pressure, a rising bar for product innovation and a complicated expanding global market.

"The new Teva will have less of some things and more of others," he said. "Our focus is to reduce complexity to optimize our cost position to become much more efficient," Dr Levin said.

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Bad-mouthing emerging biosimilars seen as big pharma sabotage tactic

Attempts to talk down the potential of biosimilars from emerging markets (scripintelligence.com, 27 November 2012) have been dismissed as part of Big Pharma's efforts to forestall developing nations from launching such products.

Industry experts in Asia provided a multitude of reasons, including the safety of 'copy biologics' and even historical evidence of limited-period country dominance in any industry sector, that lead them to believe that not only will emerging nations be able to compete, but also potentially to assume dominant positions in the global biosimilars arena.

Cipla said that there are already many precedents of biosimilars approved from non-EU countries, such as insulin made from a cell line completely different from the originator (yeast versus *Escherichia coli*), that have been widely accepted, improving the process, yields and quality over the original.

"I believe this is just their attempt to pre-empt China and India to launch biosimilars," a senior Cipla executive told *Scrip*, adding that other products such as human growth hormones, interferon, enoxaparin and erythropoietin too have had "no issues" in clinical acceptance and immunogenicity.

The executive, who is part of the Indian firm's R&D team, also suggested that companies like Cipla are "better poised" to develop biosimilars today than a decade ago, due to very advanced analytical tools that help in characterization, which were not available for older generation biologics.

"There is no doubt that trial costs are expensive and companies need to have deep pockets to embark on the program [for biosimilars] but as this science gets understood better, it will not be the forbidden fruit," the source added. Cipla is developing a clutch of biosimilars and had earlier announced plans to partner Desano of China in the biotech segment.

At a recent Credit Suisse healthcare conference, Ameet Mallik, head of biopharmaceuticals at Sandoz, Novartis' generics arm, suggested that biosimilars being developed in emerging countries "will have a tough time getting approval in the major markets" and that products from certain developing nations were perhaps not real biosimilars.

He said: "You often hear of products that are approved in China, India or Latin America calling themselves biosimilars. We would call them non-comparable copy biologics. These are molecules that have the same amino acid sequence but look very different."

Dr Amar Kureishi, chief medical officer and head of drug development at Quintiles Asia, explained that 'biosimilar' is a relatively new regulatory term that refers to the molecular closeness of the copy to the originator, and while some older biosimilars may not meet "today's definition", the newer biosimilars currently under development do.

"This does not mean that the older products being referred to somewhat disparagingly as 'non-comparable copy biologics' are unsafe or lack clinical efficacy. On the contrary, given the high price of biologics, these low cost copies have provided a much needed alternative in the realities of the developing world," Dr Kureishi told *Scrip*.

Companies such as Dr Reddy's Laboratories have in the past claimed that it remains the cost leader, allowing it to profitably sell biosimilars in emerging markets at 30%-50% lower prices than the innovator brand.

Datamonitor senior analyst Giles Somers added that it depends how much emerging market regulators move in line with major markets. "As long as differing characteristics from the reference brand are acceptable by regulators, physicians and patients in countries such as India and China, being a true biosimilar does not matter so much."

Dr Kureishi also observed that while until quite recently, manufacturers of the originator biologics were taking the position that no biosimilar could be guaranteed safe, it now appeared that well-established Western generics companies were proposing that only biosimilars made in the West are safe.

"Clearly, any new product whether biosimilar or novel biologic needs to prove itself safe, efficacious, and accessible. This should be the level playing field for all companies, whether in the West or in the developing world," he added.

Notably, Quintiles had stated that globalization had allowed the free movement of talent and capital – for example, monoclonal antibodies are being made in India and China by PhDs from Stanford University in the US. "It cannot be assumed that cheaper will not be as good. Cheaper will be cheaper and as good," Dr Kureishi had said then.

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Roche's Humer: 'Pharma can cut development costs 50%'

Franz Humer, chair of Roche, believes the pharma industry has to fundamentally change the way it manages costs in order to survive. He believes it is possible to bring down the cost of developing a drug by 30%-50% over the next five years.

Dr Humer says he has never experienced a time of such "rapid and fundamental change" in his 40 years in the pharma industry. "Innovation takes time and comes at a price. Increasingly, policy makers all over the world are implementing tougher measures to reverse the healthcare spending curve. The question: 'Does our society still want healthcare innovation and is it willing to pay for it?' needs to be asked."

Speaking at the *FT* global pharmaceutical and biotechnology conference in London on 5 December, he told delegates that "all aspects" of cost management had to be addressed. "This industry needs a different perspective on operating costs," he stated. Companies that want to stay innovative have to move towards "leaner headquarters and smaller central functions; get rid of duplications and get rid of excessive reporting standards". The pharma industry needs the "courage" to operate in "flatter organizational structures".

Dr Humer sees simplifying organizations as critical. "I know this is easier said than done as organizations have an inherent capacity to resist change and resist simplification because it means layoffs and restructuring." However, the industry has to trust its regional offices across the world "to run their businesses". Big pharma needs to "get away from the notion that headquarters know best".

On the question of cutting the costs of drug development he said, "It would be too easy to say R&D is a black box and there's nothing we can do about it." Instead, Dr Humer believes management should be asking the following questions: "Are our research ambitions realistic? Do we have the right priorities for our size and financial resources? Do we really have to develop every produc? And how do we explain our choices to our own scientists, let alone the outside world?"

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Price boost for Indian R&D, govt mulls mandatory generic name prescriptions

India's new pharmaceutical pricing policy allows a five-year exemption from price control for locally developed medicines that are patented in the country as well as drugs produced by a new process developed through local R&D and are similarly patented.

The exemptions are aimed at encouraging domestic R&D, even as India's ministry of health and family welfare said that it will also consider making prescription of drugs by generics names mandatory.

The national pharmaceutical pricing policy 2012 (NPPP-2012), which will be implemented by India's National Pharmaceuticals Pricing Authority, specifies that new drugs patented under the Indian Patent Act, and "not produced elsewhere", if developed through indigenous R&D, would be outside the purview of price control for five years from the date of commencement of its commercial production in the country.

Formulations that involve a new delivery system developed through indigenous R&D would also be eligible for a five year exemption from price control, starting from the date of its market approval in India. A certification of innovation and R&D would require to be provided by the office of Drugs Controller General of India.

Industry sources referred to a theoretical example wherein the exemption could perhaps imply that Ranbaxy's Synriam (arterolane maleate 150mg and piperaquine phosphate 750mg), India's first new chemical entity for the treatment of uncomplicated Plasmodium falciparum malaria in adults launched this year, would not fall under price control, but then again the product is not part of India's national list of essential medicines (NLEM) 2011.

The pricing policy aims to fix prices of over 650 formulations of the 348 bulk drugs specified in India's NELM 2011. Antimalarials that figure in the NELM include chloroquine phosphate and primaquine, among others.

The Indian Pharmaceutical Alliance, which represents leading domestic firms, said that though the average profitability of the pharmaceutical industry will be impacted badly by about 25%, it is reconciled to the new policy as it moves away from an intrusive and opaque pricing regime to a more transparent system. "It balances the need for affordable medicines with the compulsions of growth and R&D of the domestic industry," Dilip Shah, IPA's secretary general, said.

The Organisation of Pharmaceutical Producers of India, which represents multinational firms, said that though the new policy makes an "immediate and significant adverse financial impact" on the industry, market based pricing is "directionally prudent" for the country in the longer term. "It is expected to help improving both affordability and availability of medicines. Such a policy along with the government initiative to make essential medicines available free of cost through public hospitals and health centers will benefit all sections of the society, giving a boost to overall consumption of medicines in India," OPPI's director general, Tapan Ray, said.

A separate government committee is already looking into the issue of prices of internationally patented drugs and industry had earlier decried any attempt to use a per capita income-linked reference pricing model for this purpose.

The new market-based pricing policy [as against the previous cost-based one] fixes ceiling prices of NLEM medicines by using a simple average price of all the brands with a market share (on the basis of moving annual turnover) of 1% or more of the total market turnover of that medicine. There will be no separate ceiling prices for imported medicines that fall under the span of control.

Firms could set their product prices equal to or below the ceiling price, which is to be fixed on the basis of 'readily monitorable' market-based data. To begin with, IMS Health data would be referred to, though in the case of drugs not covered by IMS, the National Pharmaceutical Pricing Authority could collect such data by commissioning it.

These details came ahead of a Supreme Court hearing in a case concerning the pricing policy, which was adjourned to 12 December after the government sought time to place the details before the court. The All India Drug Action Network, an independent network of NGOs working to increase access and improve the rational use of essential medicines, had earlier expressed concern over the shift to a market based mechanism for price control from a cost-based one.

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Four years late, Lilly's solanezumab stays in PhIII

The earliest possible date that solanezumab is likely to reach the US Alzheimer's market is now the end of 2017, four years later than Eli Lilly had initially hoped when it started its EXPEDITION clinical trial program. Assuming approval in mild Alzheimer's disease, with additional off-label use in MCI patients, *Datamonitor* forecasts solanezumab to achieve sales of $4 billion across the seven major markets (the US, Japan, France, Germany, Italy, Spain and the UK) in 2021.

That is because Lilly is to test its experimental Alzheimer's antibody in another Phase III trial, targeting mild patients only. Discussions with the FDA dissuaded Lilly from seeking approval with a mild-to-moderate indication. The path to market for the much-maligned drug now appears relatively straightforward, albeit later than scheduled.

Almost four months after the announcement of inconclusive data from the EXPEDITION program in mild-to-moderate Alzheimer's disease, in which the primary endpoints of both trials were not met, Lilly sounded out regulators on the possibility of filing based on favorable pre-specified pooled analyses. Across both studies, solanezumab treatment slowed cognitive decline by 34% compared to placebo (p=0.001), with an additional non-significant 17% decrease in functional decline (p=0.057).

However, rather than seeking FDA approval based on the weak EXPEDITION dataset, Lilly will conduct an additional Phase III trial in patients with mild Alzheimer's disease, beginning Q3 2013. Just one additional study indicates that the FDA is willing to accept a Biologics License Application (BLA) supported by the pooled EXPEDITION data, assuming the new trial is positive.

However, as only one of the two completed Phase III trials revealed a significant cognitive benefit in mild patients, a crude estimate of success would be no higher than 50%.

This now suggests that solanezumab's path to the US market is straightforward, with its prospects hinging on the additional Phase III trial. Lilly has not yet ruled out filing solanezumab in other markets, although regulators in the other major markets are likely to also exercise caution.

http://bit.ly/VLGhOR

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Pharma fashion: Roche, Elan, LEO and Alkermes model the austerity collection

Roche brokers, Elan bifurcates, LEO stalks patients, Alkermes cleans out the prisons: those, in brief, are just four twists on the pharma business model that demonstrate how hard drug companies are working to try to find traction under increasingly discouraging market conditions.

"White pills in Western markets" models (GSK CEO Andrew Witty's phrase) are passé, eroded by pricing, budgetary and regulatory pressures. But it is possible to find a positive way forward even from conditions of adversity.

Some pharma companies are getting imaginative in their attempts to steer a commercial path in the new environment, and to exploit new market opportunities, most notably in emerging markets.

priming the pump

First, Roche and brokerage. There is a huge patient population in China that could benefit from Roche's cancer drugs, but a major barrier to Roche getting the most out of this market is the inability of most patients to pay. In an ingenious move, Roche has teamed up with insurance firm Swiss Re to build a market in China for private cancer therapy insurance.

To overcome the basic problem that regulations in China prevent foreign firms from selling insurance direct to Chinese customers, Swiss Re is offering reinsurance to domestic insurers for private cancer insurance policies for Chinese customers. To enable it to do this, Roche supplies Swiss Re with statistical data on cancer disease incidence, outcomes, treatment pathways and costs, which Swiss Re uses to calculate risks and costs, then create and price policies for local insurers. The aim is to reach 12 million people, or 1% of the Chinese population, by the end of 2013; 6 million have already reportedly signed up.

Roche has no direct financial interest in the revenues Swiss Re gets from the sale of insurance policies, and it could be opening up the market for firms with rival drugs (its own drugs are not privileged under the partnership). However, with many Chinese patients currently unable to afford its treatments, this move has the potential to open up the market in a big way for Roche.

going beyond the product

LEO Pharma is demonstrating a whole other dimension of intensity in ensuring that its drugs actually make an impact in the market. LEO Pharma is a fairly small Danish firm that is aiming to make big waves in the world of dermatology. It makes products like Daibovet/Dovobet/Taclonex (calcipotriol/betamethasone dipropionate) to treat psoriasis and Picato gel (ingenol mebutate) for actinic keratosis. Like many other specialty pharma firms it has focused on improving drug administration for patients, shortening the duration of treatment and speeding up the absorption time, for example.

But what interests us here is that the firm is a great example of how a pharma company can build into 'adjacencies' to boost its appeal to payers and patients alike.

LEO Pharma's work in the market and the clinic means it understands some key issues for patients. Firstly, the impact of such conditions goes beyond the direct physical symptoms of the disease: the social and psychological repercussions can be far more upsetting for sufferers. Secondly, keeping up with treatment programs can be difficult when they pose practical difficulties, and patients need better products and better support to improve the benefits of treatment.

Taking this insight, LEO has carried out extensive studies (even having anthropologists live alongside patients) to help it build patient care solutions that are tailored to markets and individuals and which offer value to patients and payers alike over and above the simple medicinal product.

It provides integrated clinics, text messaging services, nurse hotlines and more all around the world, and it is carrying out clinical trials to compare the benefits of treatment with and without its care initiatives. Being able to demonstrate added value and working proactively in the healthcare space to improve patient compliance and outcomes is a great way of tackling the huge problem of how to secure a place for your product at a price that covers the costs of R&D in markets that are hostile to drug spending.

here be dragons

We come to Elan. For a few years now, there has been a steady rumbling around the pharmaceutical sector. It is the sound of the industry's observers and commentators wondering how long companies can continue diverting vast sums of money towards highly risky early-stage discovery and development even as the potential for blockbuster returns from the few drugs that make it to market diminishes.

Many reports have speculated on the likelihood or imperative that companies will have to focus on what they do best and drop the rest; that big pharma will essentially become big marketing machines, retaining only late-stage clinical development from its R&D functions. The speculation had until recently remained just that.

It is true that firms are turning more and more to external partnerships to source new candidates for their clinical pipelines. But Elan was the company that finally bit the bullet and set off into the much discussed but still uncharted territory when in August this year it announced that it would be splitting in two.

Elan will henceforth be focused on its marketed multiple sclerosis drug Tysabri (natalizumab, partnered with Biogen Idec) and late-stage pipeline: hiving off its discovery and early pipeline assets will give it the ability to focus on optimizing Tysabri's potential (notably, in additional indications) while generating a higher operating profit.

and so to jail...

We couldn't conclude our overview of paradigm-shifting, out-of-the-box-thinking, business transformational radicalism without a nod to Alkermes. Many pharma firms proclaim that their products can procure cost savings in the health system by reducing the need for hospital stays, medical interventions and the like. Yawn, yawn! Alkermes' CEO Richard Pops reframes drug cost-benefit analysis in a much less restrictive context than mere healthcare. He reckons that Alkermes can also help cut expenditure in the prisons.

Alkermes' Vivitrol (naltrexone extended release) treats opioid dependence, a condition common to many incarcerated offenders. Mr Pops says that making the monthly injection a condition of parole or probation would reduce relapse rates, which would in turn have positive benefits on offending rates and on incarceration. Solid real-world data on Vivitrol's impact on recidivism and prisoner numbers could potentially drive sales of the drug, representing a win-win for both the company and prison authorities.

From Alkermes' almost cheeky opportunism to Roche's smart partnering with another industry in a major emerging market, our examples show that even though times are hard, the pharma industry is spoilt for choice when it comes to steps companies can take to lead their business in a fresh direction.

Rapid changes in the ecosystem in which pharma exists will no doubt throw up many more interesting examples of radical departures from the norm as companies adapt and evolve over the coming months.

http://bit.ly/R21uHJ eleanor.malone@informa.com

Business Bulletin

Isis and AZ in $1bn partnership

Isis Pharmaceuticals has announced a strategic alliance with AstraZeneca worth up to $1 billion plus double-digit royalties for the discovery and development of novel therapeutics against five cancer targets. Carlsbad, California-based Isis will get $31 million up front and is eligible to receive more than $1 billion in milestone and license fees from AstraZeneca, based on the success of four unidentified preclinical programs and the Phase I drug ISIS-STAT3Rx, which inhibits the STAT3 protein involved in tumor cell growth and survival
http://bit.ly/Zgs9UN

Sofinnova raises €240m VC fund

Sofinnova Partners of France has closed its seventh venture capital fund dedicated to the life sciences having raised €240 million ($312 million). Sofinnova Capital VII's investment strategy focuses on "funding entrepreneurs who are developing disruptive technologies or products" in the biopharmaceutical, medical device or industrial biotechnology field. The new fund has attracted institutional investors such as pension funds, fund of funds and insurance companies. Sofinnova Capital VII's investors include the European Investment Fund, Skandia Life Insurance Company, CNP Assurances and CDC Enterprises.
http://bit.ly/V1BcS0

Innovation needed in mental health

CEO of Lundbeck, Ulf Wiinberg, is warning that the withdrawal of pharma from drug discovery in the mental health space could leave the world vulnerable in a similar manner as pharma's withdrawal from antibiotic development some years ago has done. Speaking at the FT global pharmaceutical and biotechnology conference on 5 December, he noted that the disease burden of depression, for example, should signal a "goldmine" to the pharmaceutical industry. Instead, many companies are downsizing their research or pulling out all together.
http://bit.ly/TucTyj

UMN taps Catalent for biosimilar production

No sooner had the Japanese vaccines venture UMN Pharma listed on the Tokyo Stock Exchange than it struck its first post-IPO deal, linking up with Catalent Pharma Solutions for technology for the manufacture of biosimilars. UMN did not disclose exactly which "multiple products" it intends to develop and produce under the platform deal, but did say that it will license a "broad range of biosimilar cell lines" from Catalant that use the US firm's proprietary GPEx (Gene Product Expression) retrovector technology. UMN told *Scrip* that the agreement would allow it to offer contract biosimilar production services across "any" therapeutic areas.
http://bit.ly/U9oght

UMN at the mercy of the market

The Japanese vaccines developer UMN Pharma has emerged fairly well from the first day of trading after its initial public offering on the Mothers market of the Tokyo Stock Exchange, closing around 3.8% above the offer price on 11 December. In a generally challenging market, the loss-making firm ended up pricing the IPO right at the bottom end of the initial guidance range of ¥1,300-1,600 per share, and in the event has raised ¥4.26 billion ($51.8 million) to support its pipeline and for general corporate purposes. The shares reached ¥1,349 by market close after trading as high as ¥1,385.
http://bit.ly/ZIjdaR

Pfizer sells meningitis vaccine to Nuron

Pennsylvania-based biologics and vaccines company Nuron Biotech has acquired Pfizer's Meningitec, a vaccine for the prevention of invasive disease caused by Neisseria meningitidis serogroup C for an undisclosed sum. The vaccine, which was first launched in the UK in 1999, is registered in 23 countries worldwide (including the US) and currently marketed in Australia, Belgium, France, Germany, Spain, Switzerland and the UK. Nuron's vice-president of marketing and business development, Richard Dinovitz, said: "We are planning to expand into markets with unvaccinated and under-vaccinated populations."
http://bit.ly/V4JQ6y

Sarepta nets $118m to progress pipeline

Capitalizing on the enthusiasm for its Duchenne muscular dystrophy (DMD) drug eteplirsen, Sarepta Therapeutics priced an underwritten public offering of common stock on 13 December at $25.25 per share to raise $125 million for its exon-skipping therapies and other programs. In mid-day trading on the Nasdaq, Sarepta declined less than 1% as investors brought the stock closer to the company's asking price for its offering of 4.95 million shares. Cambridge, Massachusetts-based Sarepta will net $118.2 million after fees and before the sale of 742,574 additional shares for overallotments following the offering's 18 December close.
http://bit.ly/W2SPrq

Biogen and Isis link again

Isis Pharmaceuticals has opportunities to earn up to $1.2 billion in upfront and milestone payments plus royalties on drug sales from Biogen Idec now that the partners have entered into their third collaboration this year. Carlsbad, California-based Isis received $30 million up front to discover and develop three antisense drugs against undisclosed targets in the treatment of neurological or neuromuscular disorders. If Biogen Idec exercises options to license the assets, the company will pay up to $200 million in-license and regulatory milestone fees per drug candidate as well as double-digit royalties on drug sales.
http://bit.ly/Uf5rWm

Eisai's global production re-jig

Eisai is continuing to shake out its worldwide manufacturing operations with a decision to lease out and possibly divest to Biogen Idec part of its production facilities in Research Triangle Park in the US. The deal appears to be aimed mainly at utilizing excess capacity in the oral solid dose plant at the North Carolina site, amid sharply lower sales of Eisai's Alzheimer's disease therapy Aricept (donepezil) in the US due to generic competition. Financial details of which were not disclosed.
http://bit.ly/12xouRy

Pernix's $25m purchase of Somaxon

Somaxon Pharmaceuticals climbed 80.3% higher on the Nasdaq to close at $2.65 per share on 11 December as investors reacted to the news that Pernix Therapeutics Holdings would buy the San Diego-based developer of the prescription insomnia drug Silenor (doxepin) for $25 million in Pernix stock. Somaxon garnered $11.7 million in revenue during the 12 months ended 30 September from sales of Silenor, which launched in 2010, and Pernix anticipates that it can achieve $10-15 million in Silenor sales annually. The transaction is a continuation of the company's aggressive strategy to build up its branded and generic drug portfolio.
http://bit.ly/128lUSF

Walmart lobbies in India

Lobbying disclosures of supermarket chain Walmart have created a furore in India this week, but pharmaceutical industry experts claim that all the fuss over what's a "perfectly legitimate activity" in the US is perhaps uncalled for. Moreover, several Indian firms across sectors, including Ranbaxy Laboratories and Sun Pharmaceutical Industries, have also invested in such activity in the US. Ranbaxy is said to have paid $90,000 to Patton Boggs LLP towards current and anticipated lobbying issues. Similarly, Sun Pharma contributed $30,000 to the lobbying firm Winston & Strawn LLP for certain issues including matters relating to 'citizen petitions filed at the FDA with the effect of keeping generic drugs from timely entering the market,' a document registered in 2008 said. Both Ranbaxy and Sun declined to comment on the issue.
http://bit.ly/SKVK73

Medicines Co boosts hospital presence

The Medicines Company will make an initial investment of $300 million to expand its hospital presence with the $185 million purchase of Incline Therapeutics and its Ionsys system for the short-term management of acute post-operative pain, as well as $115 million in collaboration and option fees for a two-year exclusive global license to market the topical hemostat Recothrom from Bristol-Myers Squibb. Based on its Incline acquisition and Recothrom license announcements, The Medicines Company's stock gained $0.74 on 12 December to close up 3.4% at $22.59 per share on the Nasdaq, bringing its market cap to $1.2 billion.
http://bit.ly/TXE31X

Threats and opportunities for generics in Italy

The Italian pharmaceutical market is a tough one for investors right now, thanks to the country's economic crisis and strict price and spending controls of bureaucracy. But despite the obstacles, there is room for growth in the generics market, says "Italy Healthcare System and Drug Regulatory Analysis," a report from *Datamonitor Healthcare*.

Compared with other markets, generic penetration in Italy has been low and the market is small, estimated to be worth just €1.2 billion in the 12 months to April 2012, says the report. But there has been considerable growth recently. In 2001, generics took just 1% of the market in volume, but by 2012 this share had risen to 14.7%. Between 2001 and 2008, year-on-year volume and value growth reached 39% and 37% respectively, and between 2011 and 2017, the market should show a compound annual growth rate of 5.4%.

Generics companies have come up against a number of challenges. Traditionally, Italian patients have remained loyal to branded medicines, even after patent expiry, and have been reluctant to switch to products that could be perceived as being inferior. Misinformation about generics has also led to perceptions of inferiority, while doctors and pharmacists have lacked incentives to prescribe and dispense generics.

Generics companies will still have to get around brand loyalty, but this could be easier given that austerity-minded AIFA, Italy's regulator and pricing body in one, is trying to give the image of generic medicines a boost.

New regulations oblige doctors to write the generic name on prescriptions, something that is expected to boost uptake. Volume will also be driven by price cuts that will not only save money but also ensure there is a meaningful price differential between originators and generics. However, price cuts affecting generics are a double-edged sword and companies may find it tough to offset sometimes dramatic price cuts with higher volumes.

Companies should also be able to capitalize on AIFA's attempts to boost biosimilars. This year it put out for consultation a concept paper aimed at explaining biosimilars to healthcare professionals and the public. Steady growth in the sector is expected over the next five years given that biologics are among the most expensive drugs and as more major drugs come off patent. However, biosimilars will come up against the same challenges that generics have, such as brand loyalty and doctor resistance. Moreover, automatic substitution with biosimilars is not allowed in pharmacies.

Datamonitor report **http://bit.ly/Tu8VFZ**
Full story **http://bit.ly/TrlsKI**
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Pharma united against Alameda drug disposal law in US

Nothing unites sometime-adversaries like an issue that threatens to drain money from both sides. In this case, brand-name and generic drug makers have come together to fight a first-of-its-kind US ordinance in Alameda County, California that requires pharmaceutical manufacturers to design, implement and pay for a program to collect and dispose of unused prescription pills.

The Pharmaceutical Research and Manufacturers of America (PhRMA), Biotechnology Industry Organization (BIO) and Generic Pharmaceutical Association (GPhA) filed a lawsuit seeking to block the Alameda County Safe Drug Disposal Ordinance, which they say is unfair and unlike any other drug disposal law in North America.

The industry organizations want to stop the county from enforcing its ordinance starting in mid-2013 before other local or state governments adopt similar requirements.

Alameda County Board of Supervisors president Nate Miley spearheaded the ordinance to prevent accidental and intentional overdoses and to keep discarded medicines from contaminating groundwater when pills are flushed down toilets or left in landfills (scripintelligence.com, 6 March 2012). The board of supervisors approved the ordinance in July and the pharma industry lawsuit was filed in early December.

"Given the novel nature of the ordinance as the first of its kind nationally, and the important public purposes that it serves, the county is prepared to have the ordinance tested in a court of law," Mr Miley told *Scrip*.

Alameda County is in the San Francisco Bay Area and includes the cities of Oakland and Pleasanton, where several life science firms are headquartered, but the county's ordinance affects biotechnology and pharma companies around the globe.

PhRMA executive vice-president and general counsel James Spears said that PhRMA, BIO and GPhA do not oppose drug take-back programs, such as those organized on specific days by local governments, law enforcement agencies or municipal waste authorities to collect unused medications.

"If the government decides this is how they want to spend their tax dollars, it's their call, but the Alameda program is fundamentally different. It wants the prescription drug industry to design, implement, manage and fund a program," Mr Spears said.

The industry's two basic problems with the Alameda law are: 1) the requirement for pharma companies to design and implement a drug disposal program that does not hold the local government or the county's businesses responsible; and 2) the shifting of waste disposal costs from the government to pharma companies without a means for recouping the cost.

In writing their ordinance, Alameda County officials studied a law in the Canadian province of British Columbia that requires drug manufacturers to pay for a disposal program in which unused pills are collected at pharmacies. The difference between the Alameda and British Columbia requirements, Mr Spears said, is that pharma companies do not run the Canadian program and the province allows manufacturers to include drug disposal costs in the pricing for their medicines.

"There is no other take-back program – including the British Columbia program – that puts take-back responsibility on the shoulders of pharmaceutical companies. When they are managed locally, that is really the only way these programs can work," he said.

PhRMA, BIO and GPhA claim in their lawsuit that the ordinance's demands violate the commerce clause of the US Constitution, which assigns regulation of interstate commerce to the federal government.

"States can't reach out to regulate companies that have no connection with their jurisdiction other than they put products into interstate commerce and some of them happen to be sold in their jurisdiction. Also, the ordinance shifts the costs beyond their borders. The commerce clause prohibits the kind of cost-shifting that Alameda is trying to do here," Mr Spears said.

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To read this article in full, visit
http://bit.ly/Vx1Zqi

Phase forward for Mitsubishi Tanabe's Gilenya wannabe

Mitsubishi Tanabe Pharma (MTP) has taken a small but notable step forward with the development of its oral multiple sclerosis (MS) therapy MT-1303, starting a Phase II clinical program with the molecule being positioned as a successor to Gilenya (fingolimod), the erstwhile blockbuster sold globally through Novartis.

The Japanese firm will shortly begin recruitment for the 400-patient, placebo-controlled study at sites in Canada and the UK, investigating 24 weeks of administration of three doses of the sphingosine-1-phosphate receptor antagonist for the treatment of relapsing-remitting MS.

The primary endpoint of the study is total number of magnetic resonance imaging gadolinium-enhanced T1-weighted lesions, and completion is currently expected in March 2015.

MTP has so far disclosed little information on MT-1303 at R&D updates and business briefings, and there have been no partnering deals as yet given its still early stage of development. The company told *Scrip* that it had not yet settled on a firm licensing strategy for the product or whether it would retain rights in-house.

But one area where early data from the new trial will be watched closely is potential improved cardiovascular safety over fingolimod, which earlier this year became subject to stricter US monitoring requirements around the time of treatment initiation. These followed the death of a patient last year within 24 hours of receiving the first dose of the drug (scripintelligence.com, 15 May 2012).

Despite these issues and some payer concerns over costs, Novartis has said it expects global sales of Gilenya to exceed $1 billion this year. The drug was first approved in the US in September 2010 to reduce flare-up frequency and delay the progression of the physical symptoms of MS.

MT-1303 entered a Phase I development program in Japan in May and MTP is also investigating the molecule at the Phase I stage for the treatment of inflammatory bowel disease.

http://bit.ly/Xzv8SN

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Parliament vote turns EU patent dream into reality

The patenting of new drugs across the EU is about to become much easier and cheaper after the European Parliament finally gave its seal of approval to the unitary patent package. And a potential obstacle raised by Italy and Spain – the language used in the European Patent – was dismissed by one of the European Court of Justice's Advocates-General.

After three decades of negotiations, not to mention acrimonious argument and nationalistic wrangling, MEPs on 11 December voted overwhelmingly to approve the two regulations on the patent and the associated language regime, as well as an international agreement on establishing a unified patent court.

The two regulations will apply from the date that the court agreement enters into force. The agreement is expected to be signed in February next year, and it will come into force on 1 January 2014 or when at least 13 member states including the UK, France and Germany have ratified it.

The legislation still has to be formally adopted by the council, but this is a mere rubber stamp and will take place shortly, probably at a meeting of member state ministers on 21 December.

The main aim of the new regime is to cut the costs of patenting and help boost the competitiveness of EU companies. The parliament said the new system would reduce patenting costs by up to 80%, and was intended to benefit small and medium-sized companies in particular.

Under the new system, companies will be able to apply to the European Patent Office for a patent that is automatically valid in all participating member states (currently 25). Patents will be made available in English, French and German, and applications will have to be made in one of these three languages. If made in another language, they will have to be accompanied by a translation into one of these three languages.

Translation costs will be fully reimbursed for smaller firms, non-profits, universities and public research bodies. Renewal fees will be set at a level that takes account of the special needs of smaller firms.

slow progress

Progress towards agreement on the patent package has been slow and tortuous, regularly punctuated by disputes over legal, practical and language issues, not to mention nationalistic and protectionist stances on the part of certain member states.

Even now, only 25 of the 27 EU member states are party to the patent scheme, Italy and Spain having decided to stay on the sidelines over language issues.

The most recent falling out came earlier this year when EU heads of state decided to remove from the two draft regulations some key articles regarding the role of the Court of Justice of the European Union (CJEU) in the new system. MEPs postponed their vote on the package pending further negotiations, and did not relent until November when the member states reached a compromise solution to insert the disputed clauses into the text of the draft patent court agreement.

On the same day as the parliament's vote, the patent avoided another potential stumbling block when an advocate general of the CJEU recommended the dismissal of actions brought by Italy and Spain seeking to annul a Council of Ministers decision that authorized the use of the "enhanced co-operation" procedure to allow the 25 other member states to press ahead with the patent plan.

According to the two countries, this decision was invalid for a number of reasons. They said that the council lacked competence to adopt the decision, misused its powers and failed to respect the judicial system of the EU. They said it would also be detrimental to the EU internal market and distort competition, and that it did not respect the two countries' competencies, rights and obligations.

Addressing each point in turn, advocate-general Yves Bot recommended that the Court should reject all the pleas put forward by Italy and Spain and should consequently dismiss both actions. While advocate-general's opinions are not binding, the court generally follows their recommendations.

http://bit.ly/Uuomx2

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R&D Bites

CHMP triple approval

The EMA's Committee for Medicinal Products for Human Use (CHMP) has recommended three new therapies this month. Alexza Pharmaceuticals' antipsychotic Adasuve (loxapine) has been recommend by the CHMP for the rapid control of mild to moderate agitation in adult patients with schizophrenia or bipolar disorder. However the CHMP recommends administration in a hospital setting. Roche's targeted breast cancer drug Perjeta (pertuzumab) received a recommendation from the committee for use in combination with Herceptin and docetaxel in patients with HER2-positive metastatic or locally recurrent unresectable breast cancer. Furthermore, Lundbeck's Selincro (nalmefene) to treat alcoholism has also garnered a CHMP positive opinion.
http://bit.ly/UObySU

Genzyme/Isis to appeal CHMP block

Genzyme (a Sanofi unit) and its partner, Isis Pharmaceuticals, were disappointed at the negative opinion adopted by the CHMP on Kynamro (mipomersen) for the treatment of homozygous familial hypercholesterolemia. Kynamro is an antisense agent that acts by inhibiting the synthesis of the ApoB100 protein, which is involved in the production of LDL particles. The companies plan to request re-examination of the recommendation.
http://bit.ly/Vx1Zqj

Vanda antipsychotic rejected by CHMP

The CHMP has surprisingly blocked Vanda Pharmaceuticals' atypical antipsychotic Fanaptum (oral iloperidone tablets) for schizophrenia, raising a question over 'safety creep´ at the agency over the last decade. Charlotte Mackey, lead analyst at *Datamonitor*, told *Scrip* that the decision was "unexpected" in view of the drug's approval by the US FDA in May 2009 in the same patient population and, perhaps, also because the drug was granted market approval in Israel and Argentina earlier this year. Vanda, based in Washington, DC, intends to appeal the opinion and request a re-examination of the decision.
http://bit.ly/SL4UQO

Biotie awaits Parkinson's drug decision

Biotie Therapies has reached an anticipated key inflection point in its business after its Parkinson's disease drug, tozadenant (SYN115), met both primary and multiple secondary endpoints in a Phase IIb study. The company said it was "extremely pleased with the results of this study", adding: "We look forward to analyzing the results in detail with our license partner UCB and expect a decision from UCB in the first quarter of 2013 regarding the next steps."
http://bit.ly/RzHded

Phase IIb promise for mogamulizumab

Kyowa Hakko Kirin's mogamulizumab has shown efficacy in two forms of non-Hodgkin's lymphoma in a Phase IIb Japanese development program. The results pave the way for further trials and potentially for expanded use of the firm's first therapeutic antibody. The first-in-class anti-CCR4 (CC chemokine receptor 4) product had its first launch worldwide in Japan in May, as Poteligeo, for the orphan indication of relapsed/refractory CCR4-positive adult T-cell leukemia/lymphoma (ATL) in patients who have completed prior chemotherapy.
http://bit.ly/RzHded

AZ's new RA drug pales against Humira

AstraZeneca has failed in its bid to outshine Abbott's Humira (adalimumab) with fostamatinib, the first oral spleen tyrosine kinase (SYK) inhibitor in development as a novel oral therapeutic approach for rheumatoid arthritis (RA). It is now unclear whether the company will continue with plans to develop the drug as a monotherapy. "A more detailed analysis of the OSKIRA-4 findings will be published in due course," said AstraZeneca.
http://bit.ly/UXsgNj

GSK in $335m deal with MD Anderson

The University of Texas MD Anderson Cancer Center is continuing its legacy of licensing oncology discoveries to pharmaceutical companies via a collaboration with GlaxoSmithKline through which the cancer center may earn more than $335 million in upfront and milestone payments plus royalties on sales of therapeutic antibodies that activate OX40 receptors on the surface of T cells to mount an immune system attack. The collaboration and license agreement is the first such pact for the new Institute for Applied Cancer Science (IACS).
http://bit.ly/SFisgS

PhIII AML trial for volasertib

Boehringer Ingelheim expects to begin a Phase III trial of its investigational hematology/oncology compound, volasertib, early next year after reporting positive results from the Phase II part of a Phase I/II trial in acute myeloid leukemia at the American Society of Hematology (ASH) annual meeting in Atlanta, US. The firm said its drug showed "higher rates of objective response [the primary endpoint] and an improvement in event free survival" in newly diagnosed patients with AML receiving volasertib in combination with low-dose cytarabine (LDAC) versus LDAC alone. The company said it is also exploring further indications for volasertib with a special focus on hematological diseases.
http://bit.ly/UM5slO

US FDA nod for Zytiga

The US FDA has given the go ahead for Janssen's Zytiga (abiraterone) to be used at an earlier stage in the treatment of metastatic castration-resistant prostate cancer (mCRPC). Previously approved for use with prednisone in men with mCRPC who have received prior chemotherapy containing docetaxel, the oral, once-daily medication can now be used with prednisone ahead of chemotherapy following its expanded indication. Janssen told *Scrip*, "This expanded indication provides physicians with a proven treatment option earlier in the disease stage and offers additional hope for the approximately 35,000 men who will be diagnosed with mCRPC in the US this year."
http://bit.ly/Yc7BfV

Roche's Perjeta pricing position

Roche has released updated survival results for its new breast cancer therapy. The latest data from the 808-patient Phase III CLEOPATRA study show that using the drug together with currently used Herceptin (Roche's trastuzumab) and chemotherapy reduces the risk of death by 34% and that median overall survival in the Perjeta arm exceeds that in the control arm. *Datamonitor* noted earlier this year that Perjeta would be priced at $5,900 a month, or $71,000 a year, while Herceptin costs around $54,000 a year. While simple addition might imply a combination treatment priced at $125,000 per year, Roche´s tactic of pricing courses of treatment regardless of length may reduce this somewhat.
http://bit.ly/WioepQ

Sanofi launches Imojev for Australian travelers

Sanofi Pasteur has launched Imojev, its live vaccine against Japanese encephalitis in Australia, the product's first market worldwide and the first single-dose JE vaccine in Australia. Imojev is licensed for people from 12 months and older. The addition of a booster dose to extend the duration of protection is being assessed by the Australian Health Authorities. The drug is aimed largely at business travelers and tourists to the Asia Pacific region. Sanofi Pasteur acquired the vaccine from Acambis in 2007.
http://bit.ly/SFelRV

Celldex surges with new data

Celldex Therapeutics said additional Phase IIb EMERGE data for CDX-011 (glembatumumab vedotin) establish proof-of-principle that the antibody-drug conjugate shows higher levels of activity in breast cancer subgroups with high expression of glycoprotein NMB (GPNMB), including patients with hard-to-treat triple negative disease. The EMERGE trial enrolled 122 patients with advanced breast cancer who'd been through up to seven prior courses of therapy. The study's participants had to have at least 5% GPNMB. Investors pushed Celldex up $1.41 per share, or 25.5%, to $6.93 per share on 10 December based on the Phase IIb update.
http://bit.ly/VLFgX9

BMS' Eliquis in second indication

Following successful European approval, Bristol-Myers Squibb and Pfizer have launched the oral direct Factor Xa inhibitor, Eliquis (apixaban), in its first market – the UK – for the drug's second indication. The drug was approved last month by the European Medicines Agency for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (NVAF) with one or more risk factors and at that time Pfizer told *Scrip* that Eliquis would be available for this indication in the UK and Germany "in the coming weeks".
http://bit.ly/U4jtwW

Gilead JAKs up oncology presence with $510m YM buy

YM BioSciences surged 76.7% to close at $2.88 per share on 12 December after Gilead Sciences said it would pay $2.95 per share to buy YM and expand its oncology pipeline, valuing the Canadian developer of the selective janus kinase (JAK) 1 and 2 inhibitor CYT387 at $510 million.

The all-cash transaction, which is expected to close in the first quarter of 2013, reflects high hopes for CYT387 as a viable competitor for InCyte's JAK1 and JAK2 inhibitor Jakafi (ruxolitinib) in the treatment of myelofibrosis, based on Phase I/II data presented at the American Society of Hematology (ASH) annual meeting in December 2011. While YM has yet to begin a Phase III clinical trial, the company reaffirmed the potential for CYT387 at this year's ASH conference in Atlanta, Georgia.

Gilead plans to initiate a pivotal Phase III clinical trial for CYT387 in the treatment of myelofibrosis during the second half of 2013. Looking forward to late-stage support for the promising once-daily, oral JAK inhibitor, YM's board of directors has voted unanimously to accept Gilead's acquisition offer.

Investors appeared neutral on Gilead's plans to buy YM and advance CYT387, since the company traded down less than 1% to close at $76.23 per share on 12 December and regained all $0.11 it lost in after-market trading.

Gilead executive vice-president of research and development and chief scientific officer Norbert Bischofberger said in a statement from the company that the YM acquisition adds a complementary hematologic cancer therapy to Gilead's growing oncology portfolio.

"Based on promising Phase II data, we believe CYT387 could provide important clinical benefit for patients with myelofibrosis, including potential improvements with regard to anemia and decreased dependence on blood transfusions. We look forward to advancing CYT387 into a Phase III study as quickly as possible and to exploring its potential in other myeloproliferative diseases with significant unmet medical need," Dr Bischofberger added.

YM reported on 9 December at this year's ASH meeting that CYT387 achieved a 68% durable 12-week transfusion independence response rate with a maximal duration of response approaching three years in the 166-patient Phase I/II study.

Patients' transfusion-free periods range from 85 to 988 days and the median duration has not been reached. Also, 23% of patients who did not achieve transfusion independence had a 50% or greater reduction in transfusions. The percentage of patients requiring transfusions went from 44% at baseline to less than 10% at 40 weeks of treatment.

Most adverse events through three-plus years of treatment with CYT387 are Grade 1 reactions, with thrombocytopenia; transient, mild dizziness; mild peripheral neuropathy; and abnormalities in liver/pancreas-related laboratory tests as the most commonly reported events. And unlike Jakafi, which can cause anemia, treatment-emergent anemia and neutropenia with CYT387 remains rare.

Roth analyst Joseph Pantginis said in a 12 December report on YM's acquisition by Gilead: "This deal is in line with our expectations for YM to deliver at least a partnership or a potential buyout following the presentation of durable data for CYT387 in myelofibrosis at ASH."

Dr Pantginis noted that the YM acquisition adds to Gilead's expansion in oncology, which was helped by the 2011 purchase of Calistoga Pharmaceuticals for $375 million plus $225 million for the achievement of certain milestones.

"We believe Wednesday's acquisition of YM BioSciences goes well with Gilead's recent focus in developing novel agents for the treatment of hematologic malignancies," wrote William Blair analyst John Sonnier.

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http://bit.ly/12vJRmc

Amgen picks up deCODE to validate drug targets

Amgen will pay $415 million to enhance the Thousand Oaks, California-based biotechnology powerhouse's drug discovery and development capabilities through the acquisition of deCODE Genetics, nearly three years after the Icelandic genome sequencer emerged from bankruptcy.

Amgen spokeswoman Ashleigh Koss told *Scrip* that deCODE will operate as a Reykjavik-based subsidiary, continue to research genetic causes behind diseases and publish its findings. At the same time, Amgen will screen its early-stage molecules against deCODE's data to make sure targets reached in preclinical animal studies are valid human disease targets.

"One of the ways to truly realize the full value of human genetics is to make our research synergistic with drug development efforts where target discovery, validation and prioritization efforts can be accelerated," deCODE founder and CEO Kari Stefansson said in a joint statement from the two companies.

Dr Stefansson added: "We believe Amgen's focus and ability to incorporate our genetic research into their research and development efforts will translate our discoveries into meaningful therapies for patients."

But while deCODE has existing partnerships with other drug developers along those lines, including Pfizer, Ms Koss said it's too soon to say what future collaborations between deCODE and other companies will look like going forward in areas outside of Amgen's historical focus on cancer, kidney disease, arthritis, bone disease and other conditions.

Pfizer and deCODE entered into a collaboration in 2011 to discover gene sequence variants in the human genome associated with the autoimmune disease systemic lupus erythematosus.

deCODE went public on the Nasdaq in the US in 2000, but emerged from a November 2009 Chapter 11 bankruptcy filing in early 2010 after its acquisition by Saga Investments – an investment consortium anchored by US venture capital firms Polaris Venture Partners and ARCH Venture Partners.

Polaris co-founder and general partner Terry McGuire spoke with *Scrip* in a call from Reykjavik in which the Boston-based venture investor described the acquisition of deCODE by Amgen as a "beautiful baton pass," because deCODE's capabilities will transfer from Saga's stewardship to an investor and drug developer that is equally excited about the promise of developing drugs and treating patients based on their genomic information.

While deCODE was a good fit in Polaris' portfolio of life science companies, the venture firm would be hard-pressed to replicate deCODE's one-of-a-kind database and stature in genomic health, which includes genomic information collected from half of Iceland's population.

"I think what deCODE is doing is so unique that I don't think anyone could copy them or should copy them," Mr McGuire opined.

http://bit.ly/V3hk5q

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Distorting data or scientific disagreement? Court wrangles with free speech

The question of whether a biopharmaceutical company can claim free speech as a defense against US FDA rules governing the practice of what a firm says about unapproved indications of an approved medicine is under scrutiny at the US Court of Appeals for the Ninth Circuit in San Francisco, as it considers whether to overturn or affirm a 2009 felony conviction of InterMune's former CEO.

Dr Scott Harkonen, who left InterMune in 2003, was convicted in September 2009 of wire fraud for his role in creating and disseminating a 28 August 2002 press release that made certain claims about Actimmune (interferon gamma-1b) in treating a fatal lung disease, idiopathic pulmonary fibrosis (IPF), an unapproved indication.

The government alleged that the "fraudulent" statements in the news release were part of a scheme to boost the sales of Actimmune.

In April 2011, US District Court Judge Marilyn Hall Patel sentenced Dr Harkonen to three years of probation, with six months of home confinement, and ordered him to pay a $20,000 fine and perform 200 hours of community service – a far cry from the 10-year prison term and $1 million fine prosecutors sought.

Dr Harkonen is appealing the district court's conviction on the grounds that his statements in the press release expressed a scientific view protected under the First Amendment of the US Constitution and do not meet the criteria for prosecution under the US wire fraud laws – arguing that genuine debates over whether a given treatment caused a particular effect are outside the scope of the statute, which does not permit juries to choose one side of a scientific disagreement over another.

Oral arguments in the appeal were heard by a three-judge panel at the Ninth Circuit on 6 December, which came just days after the US Court of Appeals for the Second Circuit in Manhattan ruled that the "truthful" off-label promotion of US approved prescription drugs is not criminal activity and is protected speech under the First Amendment – throwing out the conviction of a New York sales representative for conspiracy to introduce a misbranded drug into interstate commerce related to discussions he had with doctors about unapproved uses for Jazz Pharmaceuticals' narcolepsy drug Xyrem (sodium oxybate).

Court watchers expect free speech in biopharmaceutical drug marketing to eventually make its way to the US Supreme Court.

a disagreement of views

Although InterMune's 2002 news release about a 330-patient, randomized double-blind, placebo-controlled trial acknowledged within the first paragraph that the study missed its primary endpoint of progression-free survival (PFS) in IPF, prosecutors and the FDA took particular issue with the headline: "InterMune Announces Phase III Data Demonstrating Survival Benefit of Actimmune in IPF", and its subhead, "Reduces Mortality by 70% in Patients With Mild to Moderate Disease".

The press release acknowledged that the primary "endpoint did not reach statistical significance", but said there was a trend "in favor of Actimmune-treated patients, representing an approximately 10% relative reduction in the rate of progression-free survival versus placebo".

It also said the study demonstrated a "significant survival" benefit in patients with "mild-to-moderate disease" randomly assigned to Actimmune, versus control treatment, with a p-value of 0.004, and confirmed the survival benefit seen in an earlier Phase II trial.

The firm said Actimmune also demonstrated a "strong positive trend in increased survival in the overall patient population, and a statistically significant survival benefit in patients with mild to moderate IPF".

InterMune's statement asserted there was a "40% decrease in mortality" in favor of Actimmune versus placebo (p=0.084).

"A 40% survival rate when you are testing a drug for a disease that is almost always fatal and has no approved treatment is a really remarkable, clinically significant finding," Dr Scott Harkonen's lawyer, Los Angeles attorney Mark Haddad told *Scrip*.

InterMune's statement also declared that in the 254 patients with mild-to-moderate disease, there was a "70% decrease in mortality" in favor of Actimmune versus placebo, with a p-value of 0.004, in a post hoc analysis of the study results.

Dr Harkonen was quoted in the release as stating that, "Actimmune is the only available treatment demonstrated to have clinical benefit in IPF, with improved survival data in two controlled clinical trials," and that the results will support the use of drug – with the now-former CEO estimating peak sales in the range of $400-500 million per year.

InterMune's head of clinical and medical affairs, Dr James Pennington, who left the company in 2008, said in the 2002 press release that, "We felt we had an ethical obligation to get this important news out about the survival benefit of Actimmune so physicians can evaluate it when making treatment decisions for their patients."

But Dr Thomas Fleming, a professor of biostatistics at the University of Washington in Seattle, who served as the chair of the data safety monitoring board for the study, known as GIPF-001, declared the trial results negative because the p-values for all of the pre-specified endpoints exceeded 0.05.

Not only did the primary endpoint of PFS and all nine of the secondary endpoints, including survival, fail to achieve statistical significance, "but most of them were nowhere close to achieving statistical significance", government attorneys contended in court documents.

Dr Fleming testified during the jury trial that if Actimmune had a real survival benefit, there would be at least some benefit for all patients, not just the group of patients that Dr Harkonen "chose to highlight in his fraudulent press release", prosecutors argued.

They said the data, instead, actually showed that the IPF patients outside of the chosen mild-to-moderate subgroup "actually did worse" on Actimmune than on placebo, with more of the patients on InterMune's drug dying.

While the government "has a view that because an FDA official didn't think the study was good enough to demonstrate a survival effect", Mr Haddad said, "Our point was, that was their view, but a number of other qualified individuals had a different view, and so testified at the trial."

Mr Haddad said there also were "extensive declarations" – before and after the trial – submitted to the trial court to "show that all that was being put forward as evidence of falsity was one view and not a universal view."

"To say that you can criminally prosecute and convict somebody for wire fraud because their view is inconsistent with views of others is to use the wire fraud statute in a way the Supreme Court has said it cannot be used, and it's said that for over 100 years," Mr Haddad insisted. "But if the court wants to construe the wire fraud act to reach this kind of speech, then they have to squarely confront the free speech issues. And the free speech issues are very significant."

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http://bit.ly/12kgT9D

Another letdown for Lilly as tabalumab fails in RA study

Within days of announcing a new Phase III clinical trial for the Alzheimer's therapeutic candidate solanezumab, which missed its endpoints in two previous late-stage trials, Eli Lilly said on 13 December that it would end one of three Phase III studies for tabalumab (LY2127399) in the treatment of rheumatoid arthritis (RA) due to insufficient efficacy.

Lilly vice-president of autoimmune product development Eiry Roberts said in a statement from the company that the Phase III FLEX-M study results were "unexpected" after positive Phase II results for tabalumab, an anti-B-cell activating factor monoclonal antibody.

Clinical trial enrolment has been suspended for the antibody's RA program, including two other Phase III trials, until the company completes additional analyses from ongoing RA studies in other patient populations in early 2013.

Lilly will record a pre-tax charge of $20 million to $35 million in the fourth quarter – about $0.02 per share – due to the decision to stop the FLEX-M study.

The company said on 12 December that it will initiate its third Phase III solanezumab clinical trial based on analyses of inconclusive data from the EXPEDITION-1 and EXPEDITION-2 studies in patients with mild Alzheimer's disease.

In August, Lilly ended development for the Zyprexa (olanzapine) replacement pomaglumetad methionil (LY2140023) for schizophrenia after a second Phase III pivotal trial failure for the oral glutamate 2 and 3 receptor agonist.

The decision to end the first of three Phase III RA studies for tabalumab was based on a planned interim futility analysis of the FLEX-M trial that enrolled patients with moderate-to-severe RA who had inadequate responses to methotrexate therapy. Lilly emphasized that there were no safety concerns for tabalumab and said patients enrolled in other RA studies will continue treatment with the antibody.

Phase III tabalumab clinical trials in the treatment of systemic lupus erythematosus (SLE) will continue to enrol new patients, since there is no evidence that suggests efficacy issues in the FLEX-M study will occur in the lupus trials.

"We remain committed to patients with rheumatoid arthritis and lupus and will move rapidly to evaluate the impact of these data on the overall tabalumab clinical development program," Dr Roberts said.

ISI Group analyst Mark Schoenebaum said in a note to investors on 13 December that expectations were not high for tabalumab in the multibillion-dollar RA or SLE markets, with consensus estimates among analysts at about $250 million in peak annual sales.

In terms of SLE, Dr Schoenebaum noted that tabalumab is "Benlysta-like", referring to the GlaxoSmithKline BAFF inhibitor also known as belimumab.

Benlysta was the first new lupus drug in nearly 60 years when it won the FDA's approval in 2011, but GSK is involved in a lengthy appeals process in the EU where the National Institute for Health and Clinical Excellence (NICE) in the UK has claimed that there is not enough evidence of clinical efficacy to support the therapy's high cost.

http://bit.ly/U5USYC

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FDA panel zaps Zogenix's Zohydro

The chances Zogenix would convince a US FDA panel to back approval of the firm's extended-release (ER) single-entity hydrocodone analgesic Zohydro ER were slim going into the 7 December meeting, given regulators already stated outright there is a high likelihood for abuse and misuse of the medicine.

After a day-long discussion, in which it was evident most of the members of the FDA's Anesthetic and Analgesic Drug Products Advisory Committee (ADPAC) were not comfortable with the drug's lack of an abuse-deterrent mechanism, the panel gave a resounding 'no' to Zohydro's approval – voting 11-2, with one abstention.

Trading of Zogenix's shares was halted on 7 December, but in after-hours trading, the stock plummeted about 33%, or 79 cents.

Zogenix is attempting to market Zohydro in the US as the first single-entity hydrocodone, which currently is sold only in immediate-release combination forms, generally with acetaminophen/paracetamol.

Dr Stephen Farr, president and chief operating officer at Zogenix, insisted that Zohydro would provide a hydrocodone alternative that avoids the liver toxicity that comes with the combo drugs containing acetaminophen/paracetamol.

While Zogenix consultant Dr Richard Rauck, an associate clinical professor at Wake Forest University and president of the Carolinas Pain Institute, acknowledged there is "baggage with opioids, unquestionably", he argued that Zohydro would be an "advancement in managing chronic pain".

He told the ADPAC that the population for Zohydro is likely to be "small, but a clearly defined group", which Dr Rauck described as a "sliver of a sliver" of the opioid patient population pie.

Dr Bob Rappaport, director of the FDA's Division of Anesthesia, Analgesia and Addiction Products, said the agency found no concerns with Zohydro's efficacy – a conclusion the ADPAC also affirmed, voting 8-5, with one abstention, that Zogenix demonstrated its experimental medicine is effective in managing moderate-to-severe chronic pain when a continuous around-the-clock opioid analgesic is needed for an extended period of time.

The initial vote on that question was 7-6, but one panelist said she had accidentally hit the 'no' button rather than the 'yes.'

But when it came to safety, the committee was more skeptical – voting 9-5 that Zogenix had failed to demonstrate that Zohydro ER is safe for the intended population.

Early on in the meeting, Dr Rappaport had set the stage about the agency's concerns over the potential for abuse and misuse, and the consequences of addiction, overdose and death if the FDA permits a single-entity hydrocodone ER onto the market – even if that approval came with the classwide risk evaluation and mitigation strategy (REMS) for extended-release and long-acting opioids (ER/LA).

"Regardless of the existing REMS, it can be anticipated that a single-entity hydrocodone product, in this case Zohydro ER, will contribute to already critical public health problem of prescription opioid abuse and misuse," Dr Rappaport said.

Panelist Dr Judith Kramer, an associate professor of medicine at Duke University Medical Center in Durham, North Carolina, said she was skeptical that even a stronger REMS would prohibit misuse and abuse.

Dr Kramer was among several on the ADPAC that urged the FDA not to allow Zohydro on the market until the company develops an abuse-deterrent formulation.

While the FDA has never required any drug to have abuse-deterrent features, Dr Rappaport told the panel that the agency is "actively considering under what circumstances we should require an opioid or any other highly abusable product to have abuse-deterrence for approval."

The FDA is expected to make a decision by 1 March 2013.

http://bit.ly/T5lE3b

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In NICE-land, Nexavar does not exist, so Pfizer can't compare it with Inlyta

NICE, the health technology appraisal body for England and Wales, has declined to recommend Pfizer's Inlyta (axitinib) for second line kidney cancer because Pfizer compared it with Bayer's Nexavar (sorafenib) – which NICE already rejected in 2010 – rather than best supportive care.

NICE was looking at the drug within its licensed indication, for treating advanced renal cell carcinoma, after failure of prior treatment with sunitinib or a cytokine.

NICE had specified best supportive care as the comparator, and not Nexavar, and said it was disappointed with the "lack of comparison" with best supportive care.

But Pfizer's submission was largely based on the data from the Phase III Axis trial which did compare its tyrosine kinase inhibitor with Nexavar. In that study, Inlyta extended progression-free survival with patients 6.8 months compared with an extension of 4.7 months for Nexavar ($p<0.0001$). "The committee noted that the AXIS trial was well conducted and the relevant outcomes were assessed in line with the scope of the appraisal. However, it noted the difficulties in interpreting the AXIS trial in this appraisal because of the lack of a best supportive care comparison," said NICE.

> NICE had specified best supportive care as the comparator, not Nexavar

Pfizer did include an "indirect and simulated" compassion with best supportive care using data from another trial. NICE was unhappy with the analysis and concluded that little had been done to identify uncertainties in the method and was therefore "concerned about its validity and reliability".

The institute also noted other uncertainties in Pfizer's evidence that pushed the incremental cost-effectiveness ratio beyond £50,000 per QALY.

"Before we recommend any new treatment we have to be sure the evidence on how well it works is robust and that it is cost effective. We do not want to divert NHS funds to a treatment that costs more but doesn't help people live longer," said Sir Andrew Dillon, NICE's chief executive

Pfizer had agreed a patient access scheme for the drug which would see it give a discount on the list price of £3,517 per month.

Pfizer and other stakeholders now have until 11 January to make any comments. NICE points out that the firm is free to put forward an amended patient access scheme.

NICE has not yet recommended any second line kidney cancer drugs, and it noted in its appraisal that patient experts had described the area as an unmet clinical need.

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Policy & Regulation Briefs

Will insurance exchanges be ready?

On the eve of the deadline for US states to declare whether they will run an insurance exchange, lawmakers were anything but in bipartisan agreement on the progress of implementing the programs, which are being created under the Patient Protection and Affordable Care Act to be marketplaces for reasonably priced health plans for individuals and small businesses. Indeed, Representative Henry Waxman (Democrat-California) accused his Republican colleagues of being a "Groundhog Day Congress" in their repeated attempts to take down the ACA. He declared the ACA is "the law of the land" – charging that Republicans appear to be ignoring the fact that it not only withstood a Supreme Court challenge, but a presidential election.

http://bit.ly/XKhaOi

Pfizer settles off-label promotion charges

Once again, Pfizer found itself having to pay out millions to settle charges of illegal promotion of medicines, with the latest settlements totaling about $98 million. Federal prosecutors revealed on 12 December that Pfizer will pay $55 million, plus interest, to resolve allegations its subsidiary Wyeth promoted its proton-pump inhibitor (PPI) Protonix (pantoprazole) for indications not approved by the US FDA. The medicine is approved in the US for short-term treatment of erosive esophagitis associated with gastroesophageal reflux disease (GERD). But Wyeth, which Pfizer acquired in 2009, was accused of encouraging doctors to use Protonix for all forms of GERD.

http://bit.ly/UEuG5u

Yervoy and Zelboraf get NICE nod

NICE, the health technology appraisal for England and Wales, has published final and binding guidance recommending both Bristol-Myers Squibb's Yervoy (ipillimumab) and Roche's Zelboraf (vemurafenib) for melanoma patients. Both recommendations hinge on a confidential discount offered under a patient access scheme. Yervoy is recommended for the treatment of advanced malignant melanoma in people who have received prior chemotherapy and Zelboraf is recommended for the treatment of unresectable locally advanced or metastatic BRAF V600 mutation-positive melanoma. Local NHS authorities now have three months to implement the guidance.

http://bit.ly/YcpTh3

IOM praises CIRM

The Institute of Medicine (IOM) has praised the combined efforts so far from the California Institute of Regenerative Medicine (CIRM) and its governing board, the Independent Citizens' Oversight Committee (ICOC). The state agency commissioned the IOM report to assess its operations and make recommendations on how CIRM could improve its performance. The IOM report suggested that the agency should focus now on the translation of basic science into commercial therapies with investments in – and investments by – private companies.

http://bit.ly/ZEeBCJ

US FDA adds warnings to Chantix

US drug regulators said a meta-analysis of clinical trials showed that patients using Pfizer's smoking cessation pharmaceutical aid Chantix (varenicline) experienced a higher occurrence of major adverse cardiovascular events, such as heart attacks and strokes, versus those who got a placebo. However the difference was not statistically significant. The meta-analysis incorporated data from 7,002 patients. Overall, there was a low incidence of major adverse cardiovascular events occurring within 30 days of treatment discontinuation – 0.31% for Chantix versus 0.21% for placebo.

http://bit.ly/UJd2vq

Sucampo wins broader US use of Rescula

Sucampo Pharmaceuticals won approval from the US FDA to market Rescula (unoprostone isopropyl ophthalmic solution) 0.15% for broader use as a treatment to lower intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension. The medicine originally was approved by the FDA in 2000 in a narrower population of patients intolerant of or insufficiently responsive to other IOP lowering medications. Bethesda, Maryland-based Sucampo said it intends to commercialize Rescula for the broader indication in the first quarter of 2013.

http://bit.ly/12chF8O

Pfizer's Prevnar 13 will be hard to beat as market expands

The market for pneumococcal vaccines is expected to see dynamism in the years ahead as Pfizer's latest offering, Prevnar 13, beats a path to more widespread vaccination of adults in major markets. According to the latest forecast by *Datamonitor*, sales of these vaccines in major markets will rise over the next 10 years at a compound annual growth rate of 5.2%, from nearly $2.8 billion in 2012 to $4.3 billion in 2021.

But while there will be room for other vaccines, the groundwork that Pfizer is expected to put in, establishing its product in national recommendations, will make it unlikely that rival vaccines will be able to assail its market domination.

Prevnar 13 (13-valent pneumococcal conjugate vaccine), which was approved in the EU and US in late 2009/early 2010, is expected to have sales of $2.3 billion in 2012. This figure will grow in the seven major markets of the US, Japan, France, Germany, Italy, Spain and the UK, to peak at $4 billion in 2019 with a gradual decline to $3.9 billion by 2021. The drug superseded Pfizer's Prevnar 7, covering six additional serotypes, and it is now recommended for infant vaccination.

While newly vaccinated infants make up the bulk of the market, *Datamonitor* analyst Dr Haylyn Wong believes growth will be driven by expected changes to national recommendations in the US and EU specifying the use of Prevnar 13 for routine immunization of elderly and high-risk individuals. This expansion will only begin to dampen towards the end of the 10-year period, as the cohort of adults eligible for catch-up vaccination begins to diminish.

Prevnar 13's success in the adult population, where it is expected to largely take the place of Merck & Co's 23-valent polysaccharide pneumococcal vaccine, Pneumovax (the one-time gold standard), will depend on the outcome of the large-scale CAPITA trial being run in the elderly in the Netherlands, which is expected next year. "Success of Prevnar 13 in adults is all hinged on this one CAPITA clinical trial. Each country is waiting for the results before making a decision, as physicians are eagerly waiting for a green light to use Prevnar 13 in their adult patients.

http://bit.ly/VNT4Rd

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ASH: Celgene's pomalidomide shows durable response in MM

Celgene's pomalidomide appears to produce durable responses in multiple myeloma patients who have failed previous therapies, suggest data from the pivotal Phase III MM-003 presented last week at the American Society of Hematology meeting in Atlanta.

Pomalidomide, an investigational immunomodulatory agent, is currently awaiting approval in this disease setting: an NDA for use with low-dose dexamethasone has been accepted for review by the US FDA, with a PDUFA date set for 10 February, and a decision from the EMA is expected in the second half of 2013.

Celgene is hoping that pomalidomide can replicate the success of its marketed immunomodulatory agents Revlimid (lenalidomide) and Thalomid (thalomide) in the treatment of multiple myeloma patients. In 2011, Revlimid generated sales of $3.2 billion worldwide, with Thalomid sales totaling $339 million.

Pomalidomide's good clinical efficacy, favorable safety profile and oral administration route are expected to enable the drug to gain significant uptake in relapsed or refractory multiple myeloma patients if it gains approval. Over 60% of multiple myeloma patients respond to treatment, but almost all will eventually relapse and therefore targeting this patient population is likely to gain considerable commercial reward for Celgene.

Analysts at *Datamonitor* say it is likely that Celgene will continue to position pomalidomide in the relapsed refractory setting in order to protect Revlimid's sales revenues in this indication. There are no ongoing clinical trials comparing pomalidomide to Revlimid or investigating pomalidomide as a treatment for newly diagnosed patients. This approach should allow Celgene to generate significant sales revenue from both drugs.

Although pomalidomide would face competition in the relapsed refractory setting from Proteolix/Onyx Pharmaceuticals' Kyprolis (carfilzomib), the new data from a Phase I/II study also presented at ASH suggest that the combination of these drugs may eventually prove a more attractive treatment option.

In a late-breaking abstract session, Dr Meletios Dimopoulos of the University of Athens presented data from the pivotal Phase III MM-003 open-label, multicenter trial that compared the efficacy and safety of pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone in patients who were refractory to both Velcade (Takeda/Johnson & Johnson's bortezomib) and Celgene's own Revlimid.

The MM-003 trial enrolled 455 multiple myeloma patients who had experienced disease progression within 60 days of completing their last systemic therapy. Patients in this trial had received an average of five prior therapies, and 72% were refractory to both Velcade and Revlimid. Patients were randomized 2:1 to receive either pomalidomide plus low-dose dexamethasone or high-dose dexamethasone.

Pomalidomide plus low-dose dexamethasone was found to be better than high-dose dexamethasone for the treatment of multiple myeloma patients who are refractory to both Velcade and Revlimid, with he primary endpoint of progression-free survival (PFS) being significantly improved in the pomalidomide plus low-dose dexamethasone arm: a PFS of 15.7 weeks compared with 8 weeks for patients in the high-dose dexamethasone arm.

The median overall survival (OS) for patients in the pomalidomide plus low-dose dexamethasone arm was not reached, but it was found to exceed the median OS of 34 weeks observed in patients in the high dose dexamethasone arm. Dr Dimopoulos said he expected the median OS for patients receiving pomalidomide plus low-dose dexamethasone to reach 11-12 months.

Patients in the pomalidomide plus low-dose dexamethasone arm had an overall response rate (ORR) of 16.6%, with a duration of response (DOR) of 32 weeks. These results were significantly higher than those observed with patients in the high-dose dexamethasone arm, who had an ORR of 3.9% and DOR of 28.6 weeks.

Treatment with pomalidomide was well tolerated, with no safety concerns reported. Patients in the low-dose dexamethasone arm had a lower death rate than patients in the high-dose dexamethasone arm (25% vs 38%), along with a lower rate of discontinuation of treatment (35% vs 49%). But patients receiving pomalidomide plus low-dose dexamethasone had greater hematologic toxicity, with 42% experiencing grade 3/4 neutropenia and 7% experiencing grade 3/4 febrile neutropenia compared with 15% and 0% respectively for high-dose dexamethasone patients.

http://bit.ly/UNTGaE

Aine Slowey

Sanofi mulls insulin production in India amid rising emerging markets focus

Sanofi is weighing plans to manufacture insulin in India, a move that is perhaps indicative of a significant strategic shift underway at the French giant as it gears to build on its diabetes franchise in emerging markets, where the bulk of the disease is and will be concentrated.

Sanofi is not saying much for now and told *Scrip* that the plan was a "tentative" one that is only at an "exploratory stage". "It would be premature to comment further," it said.

Sanofi, however, emphasized that the "increasing prominence" of emerging markets to its growth strategy – whether it be India or China or other emerging markets – is a 'key focus' for the group. "We are committed and will continue to be fully committed to these markets and have a long history in many of these countries – we are the number one company in this part of the world. For instance, our diabetes portfolio was further enlarged in emerging markets with the launch of Insuman SoloSTAR in Russia in July and the launch in October in India of AllStar, the first Indian-manufactured, re-usable insulin pen, manufactured by a global company in India," the company said.

Sanofi expects to make the India-made AllStar, which it said drew on the cumulative expertise of its employees across "five nations and four time zones", available to other emerging markets going forward. AllStar's development was also seen as part of early signs that the firm may be keen to embrace "reverse innovation" from emerging markets.

The Indian insulin market is estimated at about Rs10 billion ($184.3 million) and growing at about 20%. Sanofi said that its insulin business generates revenues of about Rs1.50 billion, with Lantus (insulin glargine) – the most widely used insulin globally – alone contributing more than Rs1 billion.

Of the total estimated diabetic population of 366 million in 2011, 286 million were in emerging markets and this is set to go up to 456 million in 2030, when the global diabetic population is estimated to touch 552 million. The diabetic population in developed markets is set to increase from about 80 million in 2011 to 96 million in 2030. The Western Pacific region has the largest number of people with diabetes at 132 million while the Africa region the least at 14.7 million in 2011, according to data from the International Diabetes Federation's Diabetes Atlas.

tech transfer and competition

Sanofi is said to be considering a technology transfer to vaccines manufacturer, Shantha Biotechnics, which it snapped up from Mérieux Alliance in 2009, for its Indian insulin manufacturing plans.

Sanofi, though, provided no details on capacity additions planned or existing ones, while some analysts referred to the build up in the region including Novo Nordisk's insulin facility in Bangladesh with local partner Eskayef. In India Torrent's Pharma manufactures human insulin exclusively for Novo Nordisk. The integrated manufacturing and vial packaging plant with a capacity to manufacture 26 million vials annually was commissioned in 2009. Insulin is formulated from insulin crystals supplied by Novo Nordisk, Denmark.

> Sanofi expects to make India-made AllStar available to other emerging markets

Sanofi's Frankfurt site was previously reported to be capable of meeting the insulin needs of over two million diabetics worldwide while its Russian insulin factory was projected to raise capacity to about 15 million unit dosage forms of insulin this year. In May this year Sanofi opened a new assembling and packaging line to produce pre-filled insulin injection pen Lantus SoloSTAR at its Beijing plant. Sanofi had at that time announced the second phase of the $90 million project to install a high-tech cartridge aseptic production line.

Datamonitor principal analyst Anantharaman K V said that Sanofi had faced a serious set-back when Shantha lost its WHO pre-qualification status for its Shan5 pentavalent vaccine in 2010 due to manufacturing issues which resulted in significant revenue losses. "Despite losing the WHO supply contract, Sanofi made further investments in setting up of a new manufacturing facility close to Shantha's existing site to manufacture vaccines and some of its other products. Sanofi's plans to potentially utilize this facility to manufacture insulin products including Lantus will be advantageous as the product is currently manufactured at its German plant and exported to many countries including India," he explained.

Others referred to its sharp market impact. Nimish Mehta of MP Advisors told *Scrip* that Sanofi's plans were backed by compelling business reasons and could have a significant impact on Indian players in the segment. "If they get the pricing right, they could potentially emerge as leaders in terms of profitability," Mr Mehta said. He also referred to the potential of the move to keep Sanofi away from the glare of compulsory licensing in future, given that working of a patent in India leans towards the requirement of local manufacturing.

Datamonitor senior analyst Giles Somers added that any company seriously looking to produce low cost insulin in India will potentially threaten the competitive positioning of local firms like Biocon – and also the companies it supplies bulk insulin to in the region. "The AllStar-based insulins would be set against Biocon's reusable Insupen (which is based on a device licensed from Haselmeier in Germany rather than developed in-house) and Wockhardt's Wosulin Pen Royale. To provide a competitive price, Shantha will, though, need to match the overall production yield and efficiencies of Biocon and Wockhardt," Mr Somers said. Biocon is currently ranked fourth in the overall Indian insulin market and claims to be the fastest growing insulin company in the country based on ORG IMS MAT data for August 2012.

ceiling price

But would India's dual ceiling price approach for human insulin – a lower cap for domestic manufacturers and a higher one for the imported finished form of multinationals – pose challenges for Sanofi?

Mr Somers said that together with the AllStar pen, Sanofi was positioning itself with a more affordable option to compete alongside cheaper biosimilar products. "As such, the lower pack price limit may not be an issue. However, production costs become a key factor at this end of the market and efforts to set up lower cost manufacturing could be leveraged if a more affordable product range is also to be marketed in other emerging markets such as China," he said.

India's National Pharmaceutical Pricing Authority, recently set separate ceiling prices for human insulin injection produced domestically and the imported finished form, the latter being significantly higher. For example the ceiling price of locally produced human insulin 40IU (10ml vial) has been set at Rs135.12 ($2.45) while the ceiling price for the corresponding imported version is about 18.6% higher at Rs160.26.

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Key Kyowa Kirin, DSP drugs opened up to Japan generics

The latest reimbursement price listing of generic drugs in Japan includes nine active ingredients opened up to such competition for the first time, including Kyowa Hakko Kirin's and Dainippon Sumitomo Pharma's (DSP) number two products and others from AstraZeneca and Astellas.

In all, 595 preparations from 63 firms were included in the reimbursement tariff (which allows launch) on 14 December, in one of two generic price listings annually in the country, adding to the 519 products listed in June. Kyowa Kirin's big-selling anti-allergic Allelock (olopatadine), DSP's gastroprokinetic Gasmotin (mosapride), and Astellas' atypical antipsychotic Seroquel (quetiapine; licensed from AstraZeneca), are among the major branded products that will be hit by first-time generics.

Olopatadine, Kyowa Kirin's second-biggest product in Japan after Nesp (darbepoietin alfa; licensed from Amgen) with sales of ¥21.8 billion ($261 million) in the nine months to 30 September, saw the listing of 62 products from 27 manufacturers.

In addition to mainstream firms such as Sawai and Sandoz, the generic entrants also included the generics or established product arms of several major research-based companies such as Eisai, Pfizer and Meiji Seika, in a trend over the last few such listings in Japan.

Quetiapine also came under heavy initial attack, with 60 products from 18 firms (including Sandoz, Daiichi Sankyo and Pfizer) being listed. Astellas reported sales of ¥15.1 billion for Seroquel in its fiscal first half ended 30 September.

Daiichi Sankyo's Espha generics subsidiary has taken a novel tack to add value to its generic version of the drug, using new techniques to laser print the product name and dose on both sides of individual tablets, which also carry a data barcode to help prevent medication errors. Tablet color also varies by dose to make these easily distinguishable.

25 firms launched a total of 52 preparations of mosapride, and the new competition will provide a challenge to DSP's second-highest selling product.

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Deep brain probe could leapfrog drugs in AD/neuro opportunity

Deep brain stimulation (DBS) could soon be an additional option for Alzheimer's disease treatment alongside drugs, according to a company that has just started a study testing its use in early-stage patients.

Toronto, Canada-based Functional Neuromodulation has begun a randomized Phase IIb trial, called ADvance, which will use Medtronic's Activa PC DBS systems; these are already approved in Europe and the US for other diseases including Parkinson's, dystonia, essential tremor.

Although the device is several years away from approval in Alzheimer's, it could become a more near-term treatment option while future potentially disease-modifying drugs are in development, according to the firm's president Todd Langevin.

"This circuitry-based approach could potentially be synergistic with current and future drugs," he told *Scrip*'s sister publication *Clinica*. "There's really not much out there at the moment." Currently available drugs only treat the symptoms of Alzheimer's rather than addressing its underlying causes. Several pharma companies are currently working on drugs that they hope could stop or slow the progression of Alzheimer's.

Medtronic has invested in Functional Neuromodulation, although Mr Langevin declined to say how much it had received or give more details about the terms of the agreement. Functional Neuromodulation's website states that it has raised a total of $13.4 million so far from investors Genesys Capital and Foundation Medical Partners, as well as Medtronic.

While DBS for Parkinson's is used to stimulate areas of the brain affected by the disease such as the subthalamic nucleus or globus pallidus interna, Functional Neuromodulation is trialing DBS in a brain region that is linked with memory: the fornix, which Mr Langevin described as a "reasonably accessible target".

The fornix is a white matter tract that connects to the hippocampus, which is also involved in memory. "In Alzheimer's, this circuit starts to degrade – we think of DBS as 'reactivating' the circuit," Mr Langevin explained. If this circuit has already completely degenerated, there is nothing to "kickstart" – that is why the firm is enrolling mild Alzheimer's patients in the latest trial.

But stimulating the fornix could also lead to the formation of new neurones, something that has been observed in animal studies. The ADvance trial will also evaluate this, using serial PET scans to check for brain activity; and MRI scans, to measure whether brain structures affected by Alzheimer's, such as the hippocampus, change in size with treatment.

A five-patient pilot study published in the *Archives of Neurology* in May reported that glucose metabolism, measured using PET, increased in two areas of the brain after one year of DBS treatment targeted at the fornix – Functional Neuromodulation hopes to replicate this finding in the current trial. Mr Langevin also hopes the MRI scans will demonstrate increasing hippocampal volume with DBS. "With both of these measurements, it's hard to say what it means clinically, but it certainly supports the idea that something is going on in the biology of the brain."

Several pharma players are investigating drug candidates that aim to decrease the amount of amyloid, with varying levels of success.

Earlier this month, Merck & Co announced plans to take its BACE1 inhibitor MK-8931 into Phase II/III trials; it claims the drug, a beta-amyloid precursor protein site-cleaving enzyme 1 (or beta secretase) inhibitor, is the first in its class to reach this stage of development. Other BACE1 inhibitor contenders include Lilly's LY2886721, at Phase II, and Eisai's E2609 in Phase I.

Swiss firm AC Immune claims to be about to start the first preventative study in Alzheimer's next year, with its anti-amyloid-beta antibody crenezumab, developed in partnership with Genentech. The companies also have an anti-Tau antibody in preclinical development.

However, many other amyloid-targeting Alzheimer's drug candidates have fallen by the wayside: the most recent casualty was Bristol-Myers Squibb's gamma secretase inhibitor avagacestat, which the company dropped earlier this month. In October, Lilly reported mixed data from trials of its anti-amyloid monoclonal antibody candidate solanezumab. And in August, Pfizer/Janssen/Elan discontinued another beta-amyloid-targeting drug, bapineuzumab.

In fact, the whole beta-amyloid hypothesis is coming under scrutiny, as the relationship between amyloid and Alzheimer's symptoms is still not clear; therefore, if the ADvance trial proves a success, DBS, with its different mechanism of action, could emerge as an alternative treatment.

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***Scrip*'s weekly Pipeline Watch tabulates the most recently reported late-stage clinical trial and regulatory developments from the more than 10,000 drug candidates currently under active research worldwide.**

Late-stage clinical development for the week 10-16 December 2012

Compound	Company	Indication	Mechanism of action/activity	Development status	Comments
Cancer					
Perjeta (pertuzumab)	Hoffmann-La Roche	breast cancer	epidermal growth factor receptor 2 antagonist	approval recommendation	EU
Zytiga (abiraterone acetate)	Johnson & Johnson	prostate cancer	steroid synthesis inhibitor	supplemental indication approval	US; first-line approval
Iclusig (ponatinib hydrochloride)	Ariad	chronic myelogenous leukemia	VEGFR tyrosine kinase inhibitor	first approval	US
MabThera (rituximab)	Hoffmann-La Roche	non-Hodgkin's lymphoma	CD20 antagonist	first filing	EU; subcutaneous formulation
Alpharadin (radium-223 chloride)	Bayer	castration-resistant prostate cancer	DNA inhibitor	first filing	EU
TOK-001 (galeterone)	Tokai Pharmaceuticals	castration-resistant prostate cancer	selective androgen receptor modulator	Phase II initiated	
Cardiovascular & blood					
Kynamro (mipomersen sodium)	Isis Pharmaceuticals	hypercholesterolemia	apoB-100 inhibitor	approval non-recommendation	EU
Endocrinology & metabolic					
canagliflozin + metformin	Johnson & Johnson	type 2 diabetes	sodium/glucose cotransporter 2 inhibitor	first filing	US
Infection					
BI 207127	Boehringer Ingelheim	hepatitis C infection	HCV-NS5B polymerase inhibitor	Phase III initiated	
Neurological					
Selincro (nalmefene)	BioTie Therapies	alcohol dependence	opioid receptor antagonist	approval recommendation	EU
Ophthalmological					
Rescula (unoprostone isopropyl)	Sucampo Pharmaceuticals	glaucoma	potassium channel agonist	supplemental indication approval	US
Respiratory					
Adasuve (loxapine)	Alexza	schizophrenia/bipolar disorder	dopamine receptor antagonist	approval recommendation	EU
SB010	Sterna Biologicals	asthma	GATA transcription factor inhibitor	Phase II initiated	

Source: Citeline's Pharmaprojects Pipeline

Tragic act shifts political discourse: Will there be 'meaningful action' for mental health? • Quiz show puts NIH chief to the test • Will SCOTUS take up stem cell case?

Tragic act shifts political discourse: Will there be 'meaningful action' for mental health?

Before the tragic events of 14 December at Newtown, Connecticut, in which 20 young children and six adults at Sandy Hook Elementary were killed by a gunman at their school, Congress was snarled in a bitter standoff over the fiscal cliff.

But the heated tax-and-spending debate on Capitol Hill has been placed on hold, at least during America's time of national grief, with several members of Congress joining President Barack Obama in insisting the time has come to take "meaningful action" to prevent more tragedies – "regardless of the politics".

But as lawmakers grapple not only with US gun laws – with Senator Dianne Feinstein (Democrat-California) revealing on 16 December she plans to introduce legislation in the Senate on the first day of the 113th Congress to ban the prospective sale, transfer, importation and possession of assault weapons, along with big clips or strips of more than 10 bullets – they also must determine what is "meaningful action" in addressing better access to mental healthcare in a time when those programs, including those for Medicare and Medicaid beneficiaries, are increasingly facing spending cuts.

Law enforcement emphasized over the weekend they were still piecing together the motive behind the gunman's violent shooting spree, since he had no known recorded history of criminal activity or mental illness – although some family members said the apparently very bright 20-year old had some problems – and the National Alliance on Mental Illness in a 14 December statement urged that it was "important to not make assumptions or speculate in such cases", and stressed that the "overall contribution of mental disorders to the total level of violence in society is exceptionally small".

Nonetheless, Connecticut Governor Dannel Malloy (Democrat), who called the gunman, Adam Lanza, "mentally disturbed" and a "very deeply-troubled individual", said it was time to address the nation's societal problems that led to the incomprehensible act at the Sandy Hook school – asserting that "we don't treat the mentally ill well".

"We don't reach out to families that are in trouble particularly well," Governor Malloy declared on NBC's Sunday morning political show *Meet the Press*.

But just days before the 14 December attack on the Newtown grammar school, Governor Malloy's office had been inundated with calls from angry residents in his state and groups providing mental health services about his deep budget cuts to those programs.

Indeed, on ABC's Sunday political show *This Week*, host George Stephanopoulos asserted Connecticut's public mental health system provides coverage for less than 1 in 5 residents in the state.

Governor Malloy, however, dismissed those figures, arguing that Connecticut puts a "great deal of credence and importance" on mental health.

Speaking on the same program, veteran Democratic political strategist Donna Brazile said two-thirds of states have cut services to mental health agencies.

"The burden of mental illness is enormous," Dr Thomas Insel, director of the US National Institute of Mental Health (NIMH), told lawmakers during testimony in September 2010 before the House Subcommittee on Domestic Policy. "Mental disorders can be seriously disabling, life-threatening illnesses for which we need reliable diagnostic tests, new treatments and effective strategies for prevention."

But, he asserted, "Today's treatments are not good enough."

An estimated 13 million American adults, or about 1 in 17, experience a seriously disabling mental illness each year, with those disorders the leading cause of disability in the US, Dr Insel said, noting that mental disorders, such as schizophrenia, depression and bipolar disorder, typically begin at an early age – generally before age 30.

At a 16 December evening vigil in Newtown, President Obama said he would use whatever powers his office holds to engage law enforcement, mental health professionals, parents, educators and other Americans in an effort to prevent more tragedies like what occurred at Sandy Hook, "because what choice do we have? We can't accept events like this as routine".

"We can't tolerate this anymore. These tragedies must end. And to end them, we must change," President Obama declared.

Quiz show puts NIH chief to the test

While he may have mapped the human genome, Dr Francis Collins, chief of the US National Institutes of Health, showed his knowledge of odd athletic injuries on the weekly National Public Radio comedy quiz show *Wait Wait, Don't Tell Me*.

In the weekend broadcast, which was taped on 13 December, Dr Collins also was asked whether he was pro or con hand sanitizer use – he is in favor of it – and his opinion on or medical marijuana.

"It needs a lot of study," he responded to the latter question.

Unfortunately, Dr Collins failed to win the quiz – only getting one of three questions about athletes correct.

Will SCOTUS take up stem cell case?

The Obama administration could know in January whether the US Supreme Court decides to take up an appeal by two US scientists claiming US human embryonic stem cell (hESC) funding policies harmed their work with adult stem cells by increasing competition for limited government resources – causing irreparable injury to their research.

The high court on 12 December posted a notice that the case, known as *Sherley v Sebelius*, has been distributed for the justices' 4 January 2013 conference.

There is no guarantee, however, the justices will even discuss the petition from Drs James Sherley, a biological engineer at Boston Biomedical Research Institute, and Theresa Deisher, co-founder of AVM Biotechnology, given that the Supreme Court generally only talks about a quarter of the petitions distributed for each conference – with only a few of those granted a review by the high court.

Those that are not discussed are automatically denied.

The plaintiffs are seeking to get overturned a 24 August ruling by the US Court of Appeals for the District of Columbia, which upheld the Obama administration's rules for governing how taxpayer dollars are allocated and used for hESC research (scripintelligence.com, 27 August 2012 & 15 October 2012).

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Dowsing in the life science dustbowl

What would happen to the life science universe if public market investors' appetite for early-stage risky assets never returns?

There are two alternatives for traditional life science VCs. The first is government money, while the second is the rise of the corporate venture fund.

If government funding is not the answer, then perhaps the corporate venture funds of large profitable life science companies will provide life science VCs with the lifeline they are looking for.

Funding looks likely to be in short supply for some time yet and if it takes another six years to rain again, there will be fewer VCs and far fewer private companies by the time there is another downpour.

The IPO window for life science companies is barely open on both sides of the Atlantic. The aftermarket performance of those who do manage to squeeze onto the public markets only inspires other companies who have no choice but to IPO after exhausting either their cash, their former investor's patience, or had their products returned to them by their big pharmaceutical partner.

What would happen to the life science universe if public market investors' appetite for early-stage risky assets never returns?

One of the ways we can tell that we're already in this desert in the first place is because most of those companies completing an IPO are only able to do so if their existing investors support the transaction by buying public stock. Another signpost that leads deeper into the desert is when specialist venture capitalists exit the market. With fewer investors for companies, there may be no way back to the oasis.

If it takes another six years to rain again, there will be fewer VCs and far fewer private companies by the time there is another downpour

Another recent sign that we are in the desert is the trend for VCs to retain their investments in their portfolios for much longer than was historically the case. A trickle of IPO exits means that most of the portfolio of investments in a VC's portfolio will now be built to be sold to a big pharmaceutical, diagnostic or medical device company. Unfortunately, if that was not the aim when the investment was first made, it's much less likely to be able to bash the IPO-ready, square peg investment, into the pharmaceutical round hole, although there have been one or two examples of private companies that filed an S1 as a stalking horse to a (probably already proposed) pharmaceutical acquisition.

For the rest of the venture universe that had been groomed for IPO, they are set to linger in VC portfolios where the appetite and ability for their existing investors to continue funding them looks reduced. As this scenario of longer vintage VC portfolios containing older investments persists, the old chestnut of valuation comes into play and further hinders realizations.

Private life science companies that have missed an IPO window are traditionally drip-fed cash as either loans or debt that converts up at the IPO or next private round. In either event, bridge financing keeps the valuation of many of these private companies stuck back when they may have last raised money and would be much higher than if they were raising money today. This then prevents either an exit to the public markets, or a funding round led by a new investor because the existing VCs are unwilling to take a write-down to this high valuation.

Traditionally, most VC funds have a life of 10 years which used to give them long enough to show a return. The partnerships can then raise the next fund on the back of their previous fund's performance, long before the fees from that earlier fund start drying up.

Thriving venture capital must offer an alternative to pharma

Perhaps the biggest single impact of the disappearance or diminution of public markets offerings for biotechnology companies has been the almost slavish alignment of venture capital with pharmaceutical companies.

Pioneer venture capitalists in the life sciences once invested in companies such as Amgen, Genentech, Genzyme, and Imclone. For all the difficulties they faced, these companies – when they started – shared one over-riding characteristic: they each planned to do something that pharmaceutical companies were not doing at the time. They made horrendously complex, difficult-to-manufacture- and characterize biologics that had to be infused and could not be given as white pills. Or they made drugs that addressed extraordinarily narrow markets, perhaps of a few thousand or hundreds of patients.

That they made the biologics work clinically and commercially, and that they made the orphan drugs work profitably was testimony to the validity of their original convictions (and those of their supportive venture investors). That fact that pharma didn't believe in or invest in the same development pathways meant that visionary founders (and public market investors) made a financial killing at the point that pharma embarked on its major M&A spree, having realized it could no longer pretend biologics were not pharma products.

Today though, in the virtual absence of IPOs as an exit and in the interests of financial risk reduction, venture capitalists have selected their life science investments to provide not alternatives to pharma but precise alignments with the current needs of drug companies. Pharma now provides not only VCs' exit through acquisition but also its genesis - through corporate venture investing and cornerstoning of life science funds. Increasingly few early-stage biotechnology companies have an investor profile that does not include a corporate venture contribution in an A or B round (or a discounted slice of the last round before acquisition).

In seeking greater certainty, venture capitalists cast themselves as allies of pharma. They probably do not see themselves as its lackeys, but many do.

To create real value – for the healthcare systems and patients, for their limited partners and, indeed, for pharma – more venture capital must be deployed disruptively. Pharma can make its own 'safe' investments in the heart of its current business, and can probably design them better than VCs.

Venture capital should operate in the heart of a future healthcare world, investing in vision, in alternatives, and in shaking things up a bit. Like it used to when it was successful.

One important bearish marker is that many, or even most of the previous vintage of VC funds apply to their limited partner investors for multiple extensions to this 10 year lifespan in the hope that they can eke out a better return record so that it can then be used to raise another fund. The counter argument against this is that if an investment hasn't exited the portfolio in 10 years, what is the probability that it will in years 11, 12 or 13 and return an integer (rather than fractional) multiple on cost? In part, many limited partners have responded to this extension in the time to return capital by reducing their commitments to the sector until their VCs prove themselves, although this reduced appetite may also be due to the same flight from risk that puts off public market investors from IPOs.

a decade of drought

So, let's say the there is no appreciable IPO activity, and in consequence reduced returns for life science VCs for the 10 years from 2008 to 2018. How does that scenario shape the industry? It would be a world where a few lucky privileged VCs who raised a fund in the last few years, control the market for venture funding rounds and preside over many seed-stage to public, loss-making companies desperate for cash.

Indeed, this would be The Hunger Games for life science companies, perhaps not with just one winner a year, able to survive by stabbing everyone else in the back, but there would certainly be more attrition amongst companies and VCs that can't raise money than there is today.

But even The Hunger Games scenario has structural issues since private investments are syndicated. A failure at one company means a write-down or a write-off in a number of VCs' portfolios damaging the returns of many and hindering the ability of anyone in the syndicate to raise another fund.

The Hunger Games scenario means the virtual failure for the life science VC sector as no exits at IPO and write-downs in unfundable investments prevents further fundraising and relegates many VC firms to the same sort of zombie life of Resolution Life Group. Resolution was formed to consolidate life insurance funds that were unable to take on new business and, like VC portfolios, have funding liabilities extending for many years.

> The Hunger Games scenario means the virtual failure for the life science VC sector

However, there are two alternatives for traditional life science VCs. The first is government money, while the second is the rise of the corporate venture fund. Typically, government intervention by funding life science companies is not designed to generate a financial return, but its main purpose is to generate jobs in a region, country or economic area. There is often the hope that self-sustaining businesses will emerge as a result of the funding, however the failures of Germany's Neuer Markt and the French government's investment in NiCox, as well as the historical success of the US life sciences market without much government intervention, will hardly engender further such job creation schemes.

There is the added complexity that many government funding initiatives like the seed-stage Biomedical Catalyst Fund in the UK, and the proposed Life Science Fund in Wales, are matched funded. Traditionally, VCs would wait for an academic spin-out to spend all its grants, charitable and government funding before they came in and diluted out the existing investors by leading and setting the terms for the first venture round. With matched funding, charities and governments have wised up to this dilution effect by trying to get VCs to invest at the same time (and hopefully on the same terms) as government and charities.

If government funding is not the answer, then perhaps the corporate venture funds of large profitable life science companies will provide life science VCs with the lifeline they are looking for. In days gone by, when the earliest funds at Johnson & Johnson (JJDC) and SmithKline Beecham (SROne) were trying to edge into the VC world, they would have been less sophisticated about the terms under which they invested and even the type of company as long as they could syndicate with a good investor that led to a better quality deal flow in the future.

Fast forward to today, when corporate venture funds are now staffed by former financial VCs who have been attracted to investing without the distraction of the fund-raising cycle, and the corporate VCs now know all about dictating stringent terms and excluding syndicate partners on the basis that they may be unable to fund the life of the investment.

It appears that all roads lead further into the desert as corporate VCs are now more sophisticated and more discerning than they ever were, and while they are taking up the slack left by financial VCs who can't raise a new fund, they are doing so under their own attractive terms.

Public markets are lukewarm to early-stage life science IPOs and pharmaceutical companies looking to acquire or license private biotechnology assets are increasingly looking for later and later stage validating data from their potential partners.

Funding looks likely to be in short supply for some time yet and if it takes another six years to rain again, there will be fewer VCs and far fewer private companies by the time there is another downpour.

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California-based **AP Pharma** has appointed ***Mark Gelder*** senior vice-president and chief medical officer, as the company prepares for the potential commercialization of its lead candidate, APF530. Dr Gelder most recently served as vice-president and global head of medical affairs and pharmacovigilance at GE Healthcare Medical Diagnostics.

Amgen has appointed ***Robert Bradway***, the company's CEO, chair of the board of directors. Mr Bradway has been on the board since October 2011, and has served as CEO since May 2012, having joined the company in 2006. In addition, the company has appointed ***Robert Eckert***, former CEO at Mattel and currently that company's non-executive chair, to the board, replacing ***Kevin Sharer*** who is retiring. Amgen also named ***Vance Coffman***, an Amgen director since 2007, lead independent director. All of these changes are effective from 31 December 2012.

Impax Laboratories has appointed ***Bryan Reasons*** senior vice-president and chief financial officer. Mr Reasons joined Impax in January 2012 as vice-president of finance, and has served as acting CFO since June 2012. Prior to joining Impax, he served as vice-president of finance, vice-president of risk management and general auditor at Cephalon.

TransCelerate BioPharma, a Philadelphia-based non-profit organization founded in September which aims to simplify drug development challenges and make clinical trial execution more efficient, has appointed ***Dr Dalvir Gill*** CEO, effective 1 January 2013. He succeeds ***Dr Garry Neil***, who will remain chair of the board. Dr Gill most recently served as president of Phase II-IV drug development at PharmaNet-i3.

Therapeutic antibody company **XOMA**, based in California, has appointed ***Joseph Limber*** to its board of directors. Mr Limber currently serves as president and CEO of Prometheus Laboratories, a company he joined in 2003.