SCRIP
WORLD PHARMACEUTICAL NEWS
scripnews.com July 3rd 2009 No 3452

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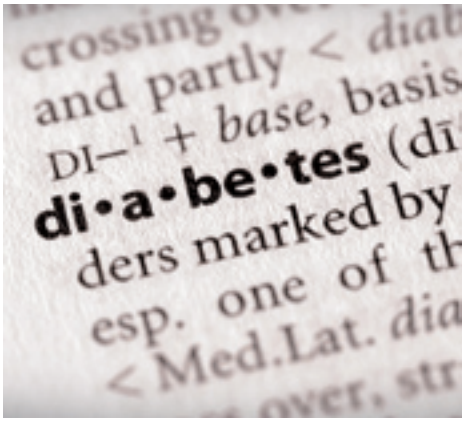
Cancer concerns overshadow Sanofi-Aventis's Lantus



DIABETES: Sanofi-Aventis's Lantus associated with cancer risk

Sanofi-Aventis's long-acting insulin analogue Lantus (insulin glargine), has been associated with an increased risk of cancer compared with human insulin in four analyses of data from patient registries in several European countries, and while the data are inconclusive, experts said that there is a case to answer. The company's shares fell on rumours during the week before the release of the data on June 26th and further upon their publication, as some analysts cut their sales forecasts for Lantus. The product was first launched in Germany in 2000 and in the US the following year, and was Sanofi-Aventis's third best-selling product in 2008, with sales of €2.45 billion.

The four studies were published in *Diabetologia*, the official journal of the European Association for the Study of Diabetes (EASD), with an accompanying editorial by Dr Ulf Smith, the association's president, and the journal's editor-in-chief Dr Edwin Gale, in which they call for further research. While they say a prospective clinical trial would be the most scientifically sound manner to proceed, they say such a trial would be slow, unfeasible and unethical. "A large combined analysis of the best available databases worldwide is the best way forward, and EASD and Sanofi-Aventis are pledged to carry this investigation forward until we have either confirmed these preliminary observations or, more hopefully, finally put them to rest."

They also, however, point out that Lantus has not been shown to be more effective than human insulin in achieving glucose control in type 2 diabetes patients. "Its main benefit (if any) is in relation to symptomatic episodes of nocturnal hypoglycaemia. We

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US FDA urged to explain its approval decisions

The US FDA should explain its approval or non-approval decisions for medicines when the action is contrary to an advisory panel recommendation, industry and consumer representatives have told the agency's transparency task force. Stakeholders said the FDA should do a better job of explaining the scientific data upon which it relies in approving drugs and making significant public health decisions. Yet there was disagreement on whether information should be released prior to a drug's approval. Consumer advocates urged that the FDA

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Japan formally approves first biosimilar

Japan's ministry of health, labour and welfare has issued its first approval for a therapeutic biosimilar, Sandoz's recombinant human growth hormone Somatropin BS (somatropin).

The move formally endorses the recent positive opinion for the product from a ministerial advisory committee (scripnews.com, June 4th, 2009).

The 5mg and 10mg injection formulations are indicated for child growth hormone deficiency and growth disorders linked to Turner's syndrome or chronic renal insufficiency. These are the same uses for which the branded reference product, Pfizer's Genotropin, is approved in Japan.

significant

The move is significant in that it shows Japan's still-evolving regulatory framework for biosimilars is now able to handle the review and approval of such products. The country's approach has taken some cues from Europe, including the use of a locally approved comparator.

Full product characterisation and the impact on safety and efficacy of any manufacturing and compositional differences are other pillars of the regulatory framework.

Sandoz said the approval further reinforced its "global leadership position" in the biosimilars market. The Novartis generics operation already markets the product as Omnitrope in the US, EU and Australia.

Somatropin BS is now undergoing reimbursement price-setting procedures and should be added to the reimbursement tariff (which allows launch) in the next few months. The exact timing of this was not yet known, Sandoz's Japanese subsidiary told *Scrip*.

In line with standard chemical generics, the product is likely to be priced at 70% of the current reimbursement level of its comparator, although again the company could not confirm this.

Sandoz already markets a wide range of generics in Japan, where its business has been built largely on the former operations of the German firm Hexal, acquired globally by Novartis in 2005.

Another biosimilar, Japan Chemical Research/Kissei's recombinant human erythropoietin, is also awaiting Japanese approval.

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Europe to lead early growth in biosimilars market

Companies looking to enter the biosimilars market will experiment in Europe before exploiting the US for greater financial returns, a new report has concluded. The European market will be the focus for firms before the US competes for most of the sector in 2014. The sector is expected to be worth $2 billion across France, Germany, Italy, Japan, Spain, the UK and the US by 2014 following patent expiries for epoetin alfa, filgrastim, interferon beta-1a, interferon alpha, human growth hormone (hGH) and insulin glargine.

Europe has emerged as a testing ground for the products with its approval guidelines in place and already marketed biosimilar drugs, according to the study by Datamonitor. The launches of hGH, epoetin alfa and filgrastim in the EU add momentum to the group's claim.

Datamonitor highlights the "generic-friendly" German market which, driven by strong payer pressures, will contribute to almost half of the biosimilars market in volume and sales through 2012. The UK will also have a high uptake of the products because of its payer pressures compared with more traditionally brand loyal markets of Italy, France, Spain and Japan.

However, beyond then the US will begin to account for a greater share of the market. By 2014, the group believes that the country will constitute nearly 90% of the seven major markets for biosimilar drugs.

"The size of the US market, combined with the voracious generic erosion that characterises it, makes it an attractive prospect for would-be biosimilars makers," said Pam Narang, a healthcare strategy analyst at Datamonitor. She added that this was dependent on establishing a biosimilars pathway, which Datamonitor believes could be in place by 2010, allowing market entry for products in 2013.

The first wave of biosimilars will reap strategic rather than financial rewards as the uptake of the products will be as reliant on the success of the public relations battle between lobbyists as it will be on tangible scientific outcomes.

While expiries to key biologics, such as epoetin alfa and filgrastim, represent the low-hanging fruit in the world of biosimilars, "they are unlikely to provide monetary gains of more complex drugs". However, they will offer manufacturers the opportunity to position themselves in the sector in anticipation of more lucrative targets.

Despite having an approval pathway for biosimilars, Datamonitor believes that the products will struggle to grow in Japan, referencing the slow uptake of small molecule products in the country, which was hindered by doubts of the quality and efficacy of generic drugs. By 2019, Japan's contribution to the seven major biosimilar markets will be 1% at most.

The group believes that historical behaviour will limit biosimilar uptake in France, Spain and Italy to the extent that they will collectively represent 25% of total market. "High brand loyalty and greater physician prescribing power mean that marketing and promotion will be critical to promoting biosimilar uptake. Therefore only the largest and more established companies, with higher brand recognition and marketing budgets are anticipated to succeed here," said Ms Narang.

The pharmaceutical industry's leading players are becoming increasingly responsive to the biosimilars market. Last year, AstraZeneca said that it was looking at developing cheaper versions of its competitors' patent expired biologics, while Merck & Co launched Merck BioVentures to develop new and follow-on biologics.

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Baxter acquires renal replacement business

Baxter is to acquire Edwards Lifesciences continuous renal replacement therapy business for around $56 million. The technology mimics the function of the kidneys throughout the day and night for patients with kidney injuries or oedema. In addition, Baxter will receive transition services from Edwards and is expected to pay it up to an additional $9 million.

Cancer concerns overshadow Sanofi-Aventis's Lantus (Continued from page 1)

have safe and effective alternatives to offer our patients with type 2 diabetes." While further research is awaited, the EASD advises that patients do not stop taking Lantus, but they can consider alternatives in consultation with their doctors, especially Profs Gale and Smith say, if they have cancer or for women if there is a family history of breast cancer.

The EMEA said that on the basis of the data "a relationship between insulin glargine and cancer cannot be confirmed nor excluded". The agency's CHMP will analyse the studies' results and any other relevant information and will also address issues, such as dose-response effects, the implications of the relatively short duration of the studies and influence of other factors on the risk of breast and other cancers.

The US FDA said it was in discussions with Sanofi-Aventis as to whether any additional studies looking at the safety and efficancy of Lantus were needed.

The American Diabetes Association called the findings "conflicting and inconclusive" and cautioned against over-reaction until more information was available.

Sanofi-Aventis said that "no definitive conclusions can be drawn regarding a possible causal relationship between Lantus and the occurrence of malignancies, as the authors of the studies point out. Clinical studies, which represent the gold standard of evidence, do not indicate an association between insulin glargine and cancer." It added that it would vigorously monitor the safety of the drug, in collaboration with regulatory agencies and scientific experts, but it was not considering a prospective, randomised clinical trial.

So far, the risk of cancer in diabetics treated with human insulin or insulin analogues has not been compared in a sufficiently powered randomised or non-randomised clinical trial, the authors of the largest of the studies in Germany say. Insulin analogues, which include long-acting insulins such as Lantus and Novo Nordisk's Levemir (insulin detemir), and short-acting insulins such as Novo Nordisk's NovoRapid (insulin aspart) and Lilly's Humalog (insulin lispro), are modified versions of human insulin that have been designed to give slow sustained release or a very rapid onset of action.

However, Sanofi-Aventis emphasised that no excessive cancer risk was seen in a randomised five-year trial with more than 1,000 patients, which compared Lantus with human insulin, although cancer was not specifically being looked for.

insulin and cancer

Cancers of the colon, breast and pancreas have all been associated with increased circulating levels of endogenous insulin in the non-diabetic population. There is a possible mechanistic basis for these findings, in that insulin is a growth factor for a number of tumours in cell culture systems, and hyperinsulinaemia also produces a secondary increase in the availability of IGF-1, another known tumour growth factor. Changes in the insulin-IGF-1 axis might be expected to favour the survival and progression of early malignant foci, supporting sufficiency in growth signals and resistance to apoptosis. Thus, while insulin may not transform normal cells to cancer cells, it is possible that it stimulates the growth of existing cancer cells. This may be consistent with the results reported from the recent studies, which detected a cancer difference within a couple of years, while cancers take many years to develop and many steps to transform healthy to malignant cells.

Insulin can bind to either the insulin receptor or the IGF-1 (insulin-like growth factor-1) receptor. The latter is the target of many anticancers in development, as its overstimulation can lead to excessive cell proliferation. The growth-promoting consequences of receptor stimulation are generally mediated by the Ras pathway, one of the most commonly mutated pathways in cancer.

The ability of the insulin analogues to stimulate human mammary epithelial cell growth generally correlates with their ability to bind to the IGF-1 receptor, but prolonged interaction with either receptor also appears necessary for stimulation of mitotic activity, Profs Smith and Gale write in the editorial. Research from 2000 by Kurtzhals *et al* in *Diabetes* found that Lantus had a six to eight-fold increase in IGF-1 receptor affinity and mitogenic potency compared with human insulin. In contrast, the two short-acting insulin analogues were reported to resemble human insulin in most respects other than a slight increase in IGF-1 receptor affinity for Humalog.

Sanofi-Aventis, however, told *Scrip* that the affinity of Lantus was still 100 times weaker than that of the native IGF-1 growth factor *in vitro*, and the type of very high Lantus concentration that would be needed to activate the IGF-1 receptor *in vivo* is not achieved in clinical use.

Initial safety concerns with Lantus were expressed some years ago because it was shown to cause some types of cells, including cancer cells, to grow and divide more rapidly in cell cultures in the laboratory. Other laboratory studies proved negative, however, so the significance of the observations has remained in doubt. It is "currently impossible to extrapolate from the *in vitro* to *in vivo* situation with any confidence", Profs Smith and Gale say, but "preclinical testing has, however, identified legitimate cause for concern regarding some of the analogues".

German study

It was the German study of almost 130,000 patients from a large insurance dataset that first sparked the current controversy over Lantus and led the EASD to recommend that three other observational analyses be conducted before its findings were published. In the study, 75% of patients were exclusively on human insulin, 19% on Lantus alone, and the rest on the short-acting insulin analogues, Humalog and NovoRapid. Levemir, more recently introduced to the German market, was not included. Almost all had type 2 diabetes.

The crude incidence of cancer was higher in patients on human insulin than in those receiving one of the three analogues, but patients on human insulin were also treated with larger doses and patients on Lantus had a much lower dose (as patients receiving combination therapy with insulin analogues and human insulin were excluded). However, after adjusting for dose, a dose-dependent increase in cancer risk was found for treatment with Lantus compared with human insulin ($p<0.0001$). The adjusted hazard ratio for a daily dose of 50IU was 1.31 (95% CI 1.20 to 1.42), as against the same dose of human insulin, representing a 31% increase in cancer risk with Lantus. In patients prescribed 50 units of Lantus daily, about 13 more patients per 1,000 would develop cancer, this suggests.

Patients taking a daily dose of 10IU of Lantus had a 9% increased risk (HR 1.09), and patients taking 30IU had a 19% increased risk. No increased risk was found for Humalog and NovoRapid. The median follow-up time was 1.63 years for cancer. There was also a higher mortality rate observed in patients treated with higher

Eurand's Zenpep faces further US delay

Eurand's pancreatic enzyme product (PEP), Zenpep (pancrelipase capsules; formerly Zentase, EUR-1008), faces a further approval delay in the US after the FDA extended the June user-fee date for the NDA by three months.

Eurand said that the agency did not request it to provide any further information, but attributed the reason for the delay to the need for additional time to review the filing.

Zenpep was the subject of an FDA approvable letter in June 2008. The letter did not require additional trials to be conducted, the company said then.

Zenpep is a proprietary PEP developed for the treatment of exocrine pancreatic insufficiency, a deficiency of enzymes that normally digest fat, protein and starch, resulting in reduced absorption of nutrients. It can occur in patients with cystic fibrosis, chronic pancreatitis, diabetes and pancreatic cancer.

Eurand says that Zenpep is a highly stable formulation of a porcine pancreatic extract that is biologically similar to the endogenous human pancreatic secretions necessary for proper human digestion.

A number of PEPs are marketed to treat cystic fibrosis, but have not been approved by the FDA, as they have been in use since before the US Federal Food Drug and Cosmetic Act came into place in 1938. In April 2004, following reports of high doses of enzymes leading to strictures of the intestines and a lack of expected therapeutic effect, the FDA told PEP manufacturers to file NDAs complying with new guidelines by April 2008, or withdraw their products from the market.

Solvay's Creon

In May, the FDA approved Solvay Pharmaceuticals' Creon (pancrelipase delayed-release) for the treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions, making it the first PEP approved under the FDA initiative aimed at getting unapproved PEPs off the market. This followed a December 2008 FDA advisory panel meeting, in which the panel said that labelling for Creon and other PEPs that are approved as drugs should warn that all porcine-derived PEPs have the potential to contain animal viruses and pose a risk of human infection, although to date there is no evidence of this having occurred. Eurand told *Scrip* that this was not the reason for the FDA's current delay, however.

The NDA for Zenpep was submitted in June 2007 and based on two Phase III trials in patients with pancreatic insufficiency and cystic fibrosis, a crossover study in 31 patients and an open-label trial in 19 children. The studies showed that Zentase produced a clinically relevant increase in the absorption of fat, protein and other nutrients, compared with placebo, which was maintained over time, and improvement in symptoms associated with impaired nutrient absorption.

It is in a Phase III trial in chronic pancreatitis patients, with results expected in the third quarter. Eurand said that the FDA did not ask for these data to be included in the filing.

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Cancer concerns overshadow Sanofi-Aventis's Lantus (Continued from page 4)

doses of Lantus (>40IU) than in patients treated with equivalent doses of human insulin (14.79 vs 9.17 per 100 patient-years).

Profs Gale and Smith say that there were a number of initial reservations expressed by the referees asked to review the publication: the biological implausibility given the short median period (1.31 years of Lantus) of exposure to each of the insulins, the lack of overall difference in cancer risk between the four insulins in the crude analysis, failure to correct for BMI in the dose-response analysis, and it not being possible to break down the finding according to tumour type - a major limitation, they say, given the low probability that any one agent might product a non-specific increase in all types of cancer.

The other studies included a Swedish study of 115,000 insulin-treated patients, 6,000 of whom were on Lantus only, which found a two-fold increase in breast cancer, but no difference in any other type of cancer.

Profs Smith and Gale say that there were study limitations, including the low number of breast cancer cases (25 on Lantus), and it was puzzling to see the effect only in the Lantus monotherapy group rather than all Lantus users. Putting the risk into perspective, they say, the added risk of breast cancer, if confirmed, would be of the order of one or two extra cases diagnosed each year for every 1,000 users.

In a Scottish study of 49,000 patients, there was again a higher number of breast cancers in women treated with Lantus alone, of about the same magnitude as that seen in the Swedish study. Again, the numbers of breast cancers was very small. The fourth study from a UK GP database found no association between cancer and the use of insulin glargine, or any other insulin. There were only about 2,000 patients on Lantus.

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US FDA urged to explain its approval decisions (Continued from page 1)

release clinical data about an investigational drug and the reasons for the agency's denial of approval, a move opposed by drug manufacturers which say it would hinder innovation.

The agency also heard calls from several speakers to make publicly available a calendar of all significant contacts between agency staff and industry personnel.

The transparency task force, led by principal deputy commissioner Dr Joshua Sharfstein, is charged with developing recommendations for making information about the agency's activities and decision-making more transparent and publicly available while still protecting confidential information as appropriate. Another public meeting is expected in the autumn. The task force's report is due in six months and could include recommendations for regulatory and legislative changes.

"make it obvious"

The trade groups PhRMA and BIO said the agency should do more to explain the drug review and approval processes to the public. "Put simply, the FDA should make it obvious to those who are interested how scientific data leads to its approval decisions," PhRMA assistant general counsel Jeffrey Francer said. "For example, when the FDA makes a regulatory decision following a public expert advisory committee meeting, the FDA should explain how the committee's recommendation factored into its decision."

The advisory panel process is "one of the great treasures of the FDA", but when the agency makes a decision different from what its outside experts recommended it is often confusing to industry and the general public, Mr Francer said. "I'm not saying this has to be part of an action letter, but some time after a decision is made and in a timely way I think it would be important to explain why the agency came to a different view ... so that people can understand the decision-making and the data the FDA relies upon to make such a decision."

Dr Diana Zuckerman, president of the National Research Center for Women and Families, said there are often discrepancies between the safety and efficacy data publicly presented by FDA staff at an advisory panel meeting and the agency's final decision on a drug's approvability. "Particularly when data are presented and re-analysed by the FDA ... and then a decision is made that is inconsistent with those data, because the data show they're not safe or ... effective and the product's approved anyway, it seems to me there should be a very simple explanation of how it is that the data presented publicly have changed and why they're different," she said.

Several consumer groups called on the FDA to release clinical trial results for unapproved products and to explain its reasons for denying approval of a particular medicine. Doing so would advance science by avoiding future clinical trials that are unlikely to be successful, protect patients and combat publication bias that favours the industry, they said.

Dr Peter Lurie, deputy director of Public Citizen's Health Research Group, said documents for drug applications under review should be made publicly available. "The FDA literally will not confirm the existence of an IND or NDA until such time as the product is either approved or it's one of those about 20% of products that appear before an advisory committee," Dr Lurie said.

"All of this is ironic because at the same time the companies are engaging in policies of selective publication, selective release to the media creating buzz for their new products, while the FDA is pretending that nothing is happening at all. In this age of the internet, bloggers and carefully orchestrated media leaks, it seems to us that the FDA's insistence on maintaining this fiction of data secrecy is particularly outmoded."

Data from a supplemental NDA that fails to win approval may be particularly relevant when the drug is already widely used off-label for that condition, said Allan Coukell, director of the Pew Prescription Project.

PhRMA's Mr Francer said any increased disclosure requirements that fail to protect innovation will damage public health. "If the FDA disclosed valuable confidential information about a product before it is approved for marketing, thereby allowing both domestic and foreign competitors to glean otherwise unavailable insight into the development process, the government would markedly decrease the incentive for development in the first place."

complete responses

Publication of complete response letters would be particularly damaging, Mr Francer said. Task force representative Jane Axelrad, the drugs centre's associate director for policy, said the agency is often urged to release complete response letters. Currently the FDA neither releases these letters nor discloses their existence. Some, though not all, companies announce receipt of complete responses, but the text of the letters is not publicly available and the public is entirely dependent upon the information released by the sponsor. Releasing these letters "would help us to be able to explain our thinking and where we are in our review", Ms Axelrad said.

However, PhRMA said public availability of such communications would harm companies and deter innovation. "I think that some of that information could be made public after approval or after withdrawal of an application, but making such information available prior to approval could give competitors unfair information about the development of a drug," Mr Francer said. He noted that critical details about how a drug is used – such as its indications, labelling, warnings and risk evaluation and mitigation strategy (REMS) – are not settled until the end of the approval process. "To provide that type of information before approval would provide competitors with insights into the development process, and those types of insights come at a development cost."

calendar

There were repeated calls during the day-long meeting to increase transparency of the FDA's contacts with industry by posting a calendar of relevant meetings between agency staff and sponsors. The agency's current public calendar lists only those meetings held by senior FDA policy makers, such as the commissioner and centre directors, with persons outside the federal government's executive branch.

BIO director for science and regulatory affairs Andrew Emmitt said agency meetings with industry are pivotal to fostering innovation and a closer look should be given to disclosing some of these interactions. However, he cautioned against inadvertently disclosing confidential information, such as when a sponsor of a currently marketed product meets a different review division about a new indication.

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Meeting

The European self-medication industry association, the ***AESGP***, plans to hold its 2010 annual meeting in Dubrovnik, Croatia, on June 9th-11th. Visit www.aesgp.be for more information about the meeting.

Fetal exposure to Depakote "needs further study"

The US FDA's paediatric advisory committee has unanimously concurred, by a vote of 11-0, with a report from agency safety researchers recommending further study of developmental delay reported in children whose mothers took Abbott Laboratories' anti-epileptic Depokote (divalproex sodium). Findings linking the medication to lower cognitive development have been considered significant because they occurred with maternal use of divalproex, but without teratogenic features.

The advisory committee meets periodically to review the impact of a number of drugs on children. The FDA's report was released in anticipation of the meeting on June 23rd.

In the memo, staff drug reviewers said that they looked at adverse events in the FDA's AERS database from approval of divalproex in March 1983 until March 2009, and found that the overall adverse event profile of divalproex is consistent with the US data sheet for the product. However, a finding of six cases of developmental delay (including two cases coded as autism) in the absence of teratogenicity "raises concern", they wrote. These cases were from foreign and domestic marketing. According to the memo, search terms in AERS indicative of development delay in the 0-10 age group included aphasia, autism, cognitive disorder, communication disorder, disturbance in attention, educational problems, learning disability, memory impairment, mental retardation and neurodevelopmental disorder.

Teratogenicity, including neural tube effects, is well described in the US data sheet for Depakote, and the product carries a "black box" warning about this risk. But developmental delay and learning disabilities associated with fetal exposure are not mentioned. FDA reviewers now indicate that the agency should also investigate the medication for ties to developmental delay problems in children exposed to the drug. Although the limitations in the reported problems make it impossible to conclude definitively that divalproex played a causal role (and genetics or other factors may have contributed), the staffers called on the FDA to study further whether such a link exists.

According to an FDA spokesperson, members of the paediatric advisory committee agreed with the agency staffers who recommended continued analysis. They requested a report back to the committee, particularly in the event of any new safety signals. Members of the committee also said they thought the FDA had enough information to go ahead and put the warning about developmental delay in infants exposed *in utero* in a "black box" now. However, when the division said it would like to review raw data and verify it before proceeding, including raw data from an *NEJM* study, the committee agreed it would be reasonable to wait.

Abbott told *Scrip*, that it has "been evaluating and discussing with the FDA the data related to developmental delay and will continue to do so in the interest of further evaluating the issue."

The study, published on April 16th in the *NEJM* (p 1,597), showed that women with epilepsy who took valproate during pregnancy gave birth to children whose IQ at the age of three averaged up to nine points lower than scores of children exposed to other epilepsy drugs, a finding independent of mother's IQ, mother's age or epilepsy type. The study, led by Dr Kimford Meador, professor of neurology at Emory University, is ongoing. Valproate is available as an intravenous form, Depacon, and Depakote becomes valproate once it has entered the body. Last month, at the American Academy of Neurology meeting, Dr Cynthia Harden of the University of Miami's Miller School of Medicine said an analysis she conducted showed an average 10-point drop in the IQ of children of mothers taking valproate.

The *NEJM* study, with its interim results, is the largest prospective study to date of long-term cognitive development in children exposed *in utero* to anti-epileptic-drug monotherapy. Dr Torbjorn Tomson of the Karolinksa Institute in Stockholm, in an editorial to accompany the study, wrote: "The study has certain limitations. It is an observational (non-randomised) study involving a selected population; it is possible that selection of the anti-epileptic drug might be associated with factors that independently predict poor cognitive development. However, a randomised trial to answer that question would pose ethical and practical difficulties, and the authors performed analyses to control for important potential confounding factors."

Dr Tomson looked at how the report should affect clinical practice. He said that for women with focal seizures, several effective alternatives to valproate are available. However, alternatives are less clear for patients with generalised epilepsies, for whom valproate has appeared to be more effective than lamotrigine or topiramate. He noted, "A low dose of valproate remains an option if seizures cannot be controlled by other drugs. Doses below 800mg per day may not be associated with fetal risks that are any greater than the risks associated with the use of other anti-epileptic drugs."

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FTC prods Merck & Co and S-Plough for more merger details

The US government has requested more information regarding Schering-Plough's and Merck & Co's proposed $41.1 billion merger. The Federal Trade Commission's antitrust review is its second query into the deal that would create the world's second largest pharmaceutical company.

Media reports have suggested that the FTC's request could prompt a sale of the animal health units. Earlier this month, the *Wall Street Journal* reported that Merck had been touting the business to potential buyers.

Last year, Merck's animal health unit Merial had sales of around $2.6 billion, while Schering-Plough's counterpart Intervet had revenues of approximately $3 billion.

Merck & Co's four-part debt offering

Amount of debt ($ bill)	Basis points over US treasuries	Years to maturation
1.25	75	2
1.00	175	6
1.25	140	10
0.75	145	30

Source: Informa Global Markets

The firms both told *Scrip* that the request was primarily related to the pair's individual animal health businesses and expected the deal to be completed, as planned, by the year-end. Both companies said that they anticipated the review and intend to cooperate fully with the commission.

Recently, *Scrip* reported that much of the regulator's focus would be on each firm's animal health business as they overlap slightly, with some scrutiny reserved for the pair's European, Brazilian and Japanese businesses (scripnews.com, May 20th, 2009).

debt offering

Separately, Merck is planning to sell $4.25 billion in debt in a four-part offering with tranches maturing between two and 30 years. According to Informa Global Markets, Merck had intended to raise $3.5 billion through the transaction, which involves Banc of America, Citigroup, JP Morgan and the Royal Bank of Scotland.

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Penwest Pharmaceuticals urged to wind down operations

Penwest Pharmaceuticals' shareholders have approved proposals that call for the closure of the company's operations. The results of the US firm's annual meeting confirmed shareholders' support for shuttering the business, which will now be considered by the board.

Penwest stakeholders have elected Joseph Edelman and Kevin Tang to the board, who will also mull over winding down the company. The shareholders voted down two bylaw amendments that would require a super-majority board approval for certain actions.

The firm has been engaged in a proxy contest with Tang Capital and Perceptive Life Sciences since May. The dissident shareholders wanted to elect three people to the board, close the company's operations and terminate the development of A0001, Penwest's compound for mitochondrial diseases. But the company wants to complete Phase Ib and IIa trials before making a decision on the product's future. Penwest expects data by the first quarter of 2010 for the co-enzyme Q10 analogue that has demonstrated improved mitochondrial function *in vitro*.

During the past few weeks, Penwest has been active on the business development front. The firm received Cdn$2 million ($1.8 million) as part of a licensing agreement with Valeant Pharmaceuticals for its pain product Opana (oxymorphone extended-release; scripnews.com, June 10th, 2009). Distributing the product's royalty stream was one of the proposals made by the dissident shareholders.

It also licensed its TIMERx oral delivery technology to Otsuka Pharmaceutical for an undisclosed compound.

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GSK and Chroma in $1 billion deal

GlaxoSmithKline could pay the UK-based private drug discovery company Chroma Therapeutics more than $1 billion to develop macrophage-targeted drugs in an agreement signed with GSK's Centre of Excellence for External Drug Discovery.

Using its esterase-sensitive motif (ESM) technology, Chroma will initiate four discovery and development programmes to identify small-molecule therapeutics, including its macrophage-targeted HDAC inhibitor programme CHR-2845 for inflammatory disorders.

ESM technology adds amino acid esters to compounds with the aim of targeting the compounds to specific cells in the inflammatory disease process, Chroma says.

GSK may choose to obtain exclusive global licences to product candidates within the programmes once Chroma has brought them through clinical proof-of-concept studies. At such time, GSK will assume full responsibility for the development and commercialisation of the products.

Chroma will retain the rights to any products in the four programmes that GSK does not choose to license.

GSK is to pay Chroma an up-front undisclosed amount and the biotech may receive milestones, option fees and tiered royalties based on compounds that arise from the deal.

GSK has also invested in Chroma's £15 million series D private financing round, which included previous investors Abingworth Management, Essex Woodlands Healthcare Ventures, Glide Healthcare, Nomura Phase4 Ventures and the Wellcome Trust. Chroma will use the funds from the round to take its aminopeptidase inhibitor tosedostat (CHR-2797) into late-stage development for the treatment for cancer, as well as to boost development of its CHR-2845 programme. Chroma had hoped that CHR-2845 would enter clinical trials by the end of last year, but it remains in preclinical studies.

The agreement is the second major deal that GSK has signed this month, following its collaboration with Concert Pharmaceuticals at the beginning of June. It paid the US private company $35 million up front to develop and commercialise three of its deuterium product programmes and could eventually pay up to $1 billion in milestones and royalties.

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Novo Nordisk adds DKK30 million settlement to alleged kickback payouts

Settlements to end Novo Nordisk's involvement in the UN oil-for-food programme kickback case have spread into Europe, with the company issuing a payout of DKK30 million ($5.6 million) to Danish authorities.

The company recently reached the settlement with the Danish Public Prosecutor for Serious Economic Crime, the specialised unit of the Danish Prosecution Service handling war crimes and crimes against humanity.

Novo Nordisk was required to settle in Denmark as it is both headquartered and holds its corporate accounts in the country.

The settlement relates to allegations that Novo Nordisk paid kickbacks to Iraqi officials as part of the UN's oil-for-food programme, which was designed to allow Iraq to put proceeds from oil sales into a UN escrow account, with which it could then purchase humanitarian goods, including medicines and food. This was proposed after international trade sanctions were initiated against the country following its invasion of Kuwait in 1990 under Saddam Hussein.

However, in 2000 the Iraqi government began requiring Novo Nordisk to pay a "kickback", termed an "after sales services fee", in order to secure contracts to provide its diabetes medicines, which the company paid until 2003. The fee was usually 10% of the contract price.

settlements

The DKK30 million settlement covers the amount the company gained in profits from the kickbacks, as calculated by the Danish authorities. Elsewhere, Novo Nordisk has already settled similar allegations in the US; the company paid more than $18 million to the US Department of Justice and the Securities and Exchange Commission (SEC) for improper payments to obtain contracts. This included $3 million in civil penalties, $6 million in disgorgement of profits, including interest, in connection with the contracts to the SEC, and a $9 million penalty as a result of a deferred prosecution agreement with the Justice Department (scripnews.com, May 15th, 2009).

Following the Danish settlement, Novo Nordisk's president and CEO Lars Rebein Sørensen said that the company had admitted making mistakes regarding the programme and was doing what [it] could to prevent similar situations in the future. This includes implementing more rigid screening of agents, more rigorous trading ethics among all employees, especially sales divisions, and a greater number of steps with which approval providers must comply, the company said.

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Meeting

Management Forum is holding a conference on ***Pharmaceutical Origination and Artwork*** in London on September 23rd-24th. For further information, visit www.management-forum.co.uk/pharmaceutical/eventid/984.

H1N1 vaccine developer faces Chapter 7 petition

Protein Sciences is being pushed to liquidate by creditors, not long after after the US company began making its vaccine against the H1N1 influenza virus. The news comes as the firm was awarded a $150 million five-year contract by the US government to develop its influenza vaccine.

The creditors have filed an involuntary Chapter 7 petition ordering the firm to be liquidated to satisfy claims of around $11.7 million. The claim, filed in Wilmington, Delaware, asked the court to appoint a trustee to replace the management at Protein Sciences.

Protein Sciences recently said that it had started manufacturing "the first and only" vaccine, PanBlok, to protect humans against H1N1 influenza virus. The company began producing up to 100,000 doses per week of the product.

influenza contract

The Human Health Services' secretary Kathleen Sebelius recently said that her department would grant Protein Sciences a $35 million contract, which could be extended by up to five years and be worth $147 million, to develop a new influenza vaccine.

If the product is safe and effective and the FDA licenses it for influenza, the contract requires a domestic manufacturing capability to provide a finished product within 12 weeks of pandemic onset and at least 50 million doses of vaccines within six months of the onset.

The firm uses recombinant DNA technology to develop vaccines by placing an influenza virus gene into an insect baculovirus.

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Eisai opens European headquarters in the UK

Eisai has opened a £100 million European Knowledge Centre (EKC) in Hatfield, Hertfordshire, to develop treatments for conditions such as Alzheimer's disease, Parkinson's disease and epilepsy.

The new 14.5 acre facility, which will also serve as the Japanese pharmaceutical company's European headquarters, will bring more than 500 jobs to the area, including around 260 in R&D. Eisai's UK sales and marketing teams will also be based at the EKC.

The EKC was officially opened by Eisai's president and CEO Haruo Naito, the Japanese ambassador to the UK Shin Ebihara, the UK Minister of State for Foreign and Commonwealth Affairs Ivan Lewis, and the author and Alzheimer's disease research campaigner Sir Terry Pratchett.

Earlier this year, the then UK secretary of health Alan Johnson met Eisai's management team in Japan, and Mr Lewis heralded the opening of the facility as a new strategic partnership between Japan and the UK. Mr Lewis stressed that such a sizeable investment in the UK was all the more important given its occurrence during a recession.

The move by Eisai is a boon for the UK government, which "has put the pharmaceutical industry at the heart of its economic agenda", said Mr Lewis. He added that the EKC is a "real sign of confidence in the direction of the UK and European economies are taking". New challenges presented by the UK's ageing population mean that a treatment for Alzheimer's disease would be one of the great achievements of the 21st century, the minister said.

an Alzheimer's tsunami

However, the UK's National Institute for health and Clinical Excellence (NICE) has been heavily criticised for refusing to update its recommendations for the treatment of mild-stage Alzheimer's disease. Its original 2006 guidance, which stated that four Alzheimer's drugs – donepezil, rivastigmine, galantamine and memantine – should only be used in the management of patients with moderately severe Alzheimer's disease, was upheld earlier this month (scripnews.com, June 11th, 2008). Eisai itself, which co-promotes the donepezil product Aricept

EISAI'S CEO HARUO NAITO: The EKC will drive the company's further growth in Europe

with Pfizer, said it had "serious concerns" about the quality of the economic model used to assess the drugs.

Sir Terry Pratchett, who was diagnosed with a rare form of Alzheimer's disease called posterior cortical atrophy towards the end of 2007, has been highly critical of NICE, under whose ruling he is too young to be prescribed Aricept – the minimum prescribing age for the product is currently 65, while Sir Terry is only 59.

The author stressed the need for an increase in the amount of research into conditions such as his.

"The next two decades will see a tsunami of Alzheimer's sufferers, all desperately hoping for a treatment which will allow them to live more easily with the condition. We need to speed up research and the speed in which successful discoveries get to patients ... I hope everyone employed (at the EKC) works overtime!" he said.

Mr Naito hopes to bring Eisai's work ethic to the Hatfield facility and said that an emphasis will be placed on social interaction to encourage the flow of ideas between employees. Indeed, the CEO said that the cafeteria will be one of the most important areas of the EKC as it is where employees are able to share plans to better the facility's operations.

The EKC has an initial capacity to produce up to 450 million tablets in 10 million packs each year, but could ultimately produce up to 800 million tablets and 28 million packs a year, Eisai said. It expects to make back the £100 million investment within the next 10 years.

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Targeted Genetics extends runway

Targeted Genetics is implementing a series of cost-cutting measures, including laying off up to half of its employees, to enable it to continue operations into August as it seeks financing. It had previously said it would run out of cash at the end of this month.

The US firm said it would meet product supply requirements using contract manufacturing organisations and as a result will reduce its total headcount to 10-15 by the end of July.

The company is also hoping to settle its Bothell lease obligations and reduce or eliminate its other facility costs.

additional capital

Targeted Genetics said it has been pursuing additional capital through strategic transactions, licensing or selling technology, product development collaborations, and sales of stock.

"If the company is not successful in raising additional funding sufficient to support ongoing operations, it will wind down its business or otherwise cease its operations," it reiterated.

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Biovitrum divests two programmes

Biovitrum of Sweden is transferring two preclinical projects to iNovacia, a young drug discovery service provider.

The first is a programme for small molecule modulation of the GPR 119 receptor to treat diabetes and the second a SCD-1 (stearoylcoenzyme-A-desaturase-1) enzyme inhibitor programme to treat obesity and diabetes.

The agreement includes a 70:30 split of all future revenues in iNovacia's favour. Biovitrum will receive royalties from any future product sales while iNovacia is allowed to form additional partnerships to further develop the projects.

iNovacia has been providing Biovitrum with molecular pharmacology and medicinal chemistry for the two programmes, chief executive Thomas Olin told *Scrip*.

"iNovacia will continue to focus on drug discovery services [and also] offer customers the possibility to access lead compounds. We see this as an extension of our current service," he added.

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Clavis raises NOK129 million on back of positive Phase II data

Clavis Pharma has raised NOK129 million (around $20 million) through a private placement of 10.75 million new shares at NOK12.00 each. The news comes following recent positive data from a Phase II trial of its lead development product elacytarabine in late-stage acute myeloid leukaemia (AML).

The placement, which represents approximately 80% of the current outstanding share capital, was oversubscribed, according to Clavis. Most of the company's existing investors participated, including NeoMed Management and MVM Life Science Partners, as well as a number of new institutional investors.

Completion of the fundraising is conditional upon approval by Clavis's EGM on July 15th.

Proceeds from the round will be used to fund the first part of a Phase II/III registration study for elacytarabine in AML. This is scheduled to start at the beginning of next year and data could be available as early as the end 2010, the company's chief executive Geir Christian Melen told *Scrip*.

"If the data from the first part of the Phase II/III study are positive, we will consider filing for accelerated approval for elacytarabine," he added.

Phase II data

In the Phase II study, 61 patients with late-stage AML who failed to respond or relapsed after two separate rounds of treatments received third-line therapy (also called second salvage) with intravenous elacytarabine. The response to treatment was compared with a historical outcome analysis of 594 similar second salvage AML patients.

Median overall survival in the elacytarabine study was three times that of the historical control patients (5.5 months versus 1.5 months).

Patients in the elacytarabine study had an overall remission rate of 15% compared with 2.5% in the control patients.

Elacytarabine was relatively well tolerated and 30-day all-cause mortality following treatment was substantially lower than published data for existing therapies (13% versus 25%).

Other milestones Clavis is aiming to fund with the cash include completing a Phase II study of its second programme, intravenous CP-4126 in pancreatic cancer. Data from this trial are expected next year.

Clavis uses a lipid vector technology to improve existing drugs by chemically binding specific unsaturated lipids, thereby creating new chemical entities. Data generated suggest that the resulting patentable NCEs offer improved efficacy and reduced side-effects through enhanced pharmacokinetic properties, greater tissue penetration and, in many cases, additional modes of action.

The company's oncology-focused portfolio also includes oral CP-4126 in Phase I and CP-4200 in early preclinical development. "We need to find the optimal commercialisation strategy for our pipeline and we are in discussions with a number of potential partners," concluded Mr Melen.

In February, fellow oncology-focused Norwegian firm Algeta raised NOK245 million in a private placement of 22.3 million new shares.

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Meeting

A symposium on the ***Batch Release for Human Vaccines: Principles, Procedures and Tools*** is being held by the European Directorate for the Quality of Medicines & Healthcare (EDQM) in Strasbourg, France, on October 15th-16th. For further information, visit www.edqm.eu/en/Batch-release-for-human-vaccines-Strasbourg-France-1167.html.

BUSINESS ROUND-UP

Cerulean Pharma has acquired an exclusive worldwide licence to **Calando Pharmaceuticals**' cyclodextrin co-polymer based drug delivery technology to develop and commercialise therapeutic products arising from the application of this technology. Additionally, Cerulean has acquired exclusive worldwide rights to develop and commercialise Calando's anticancer candidate IT-101, the lead candidate from the co-polymer drug delivery programme. IT-101 is a camptothecin nanoparticle that has completed a Phase I clinical trial.

Halozyme Therapeutics has raised $40 million in a public offering to advance its internal pipeline of product candidates. The US company's share price fell by almost 17% to $6.27 following the fundraising. The offering of 6.15 million of newly issued shares at $6.50 each will accrue net proceeds of $38.2 million. It extends Halozyme's cash position beyond the 18 months it had previously forecasted.

Takeda has formed a new global advisory board which includes four industry heavyweights with top-level international management experience. The aim is to help Japan's top pharmaceutical company shape its strategic policies. In addition to the four new external advisors, the board will comprise 10 senior Takeda executives and will meet twice a year, Takeda told *Scrip*. The first meeting is scheduled for the autumn.

Dainippon Sumitomo Pharma is to set up a new holding entity in the US next month as it prepares to build up its independent business activities in this key market. The wholly owned operation, likely to be called DSP America Holdings, will be based in Fort Lee, New Jersey, and capitalised at $23 million.

Astellas is scaling up its presence in India, seven months after it launched a subsidiary in the country. The company said that it is developing a sales and marketing set-up in India for its in-house products. The immunosuppressant, Prograf (tacrolimus), used in transplant and other settings, is the first product from the firm's stable that would be marketed by the Indian arm that was set up last year.

Novartis has raised its holding in its Indian subsidiary from 50.93% to 76.42% following the completion of its recent tender offer. Novartis's current holding, however, falls short of the 89.93% stake it expected to garner at the time of announcing the offer. The company had earlier improved its tender offer price to Rs450 ($9.40) per share from Rs351 per share. Novartis's aim for the tender offer was primarily to increase its ownership of the Indian arm.

Excel Life Sciences, a US-based India-focused clinical trial management firm and **PFC Pharma Focus**, a Swiss contract research provider, have launched a CRO specialising in clinical monitoring and data management services in India. PFC India, the new unit, will service biopharmaceutical companies and CROs with their clinical trial support needs in India and will have an office in New Delhi.

IFC, a member of the World Bank group, is providing $50 million in loans to India's **Apollo Hospitals Enterprise**, to help the group expand its hospital network to smaller cities across the country. Apollo's network of Reach Hospitals, which are designed for less-developed population centres, would be expanded, and the company expects to set up 15 new hospitals in the next three years. It also expects to create employment opportunities for local medical professionals.

Gyros hopes its recent SEK80 million (around €7.5 million) fundraising will see it through to profitability. The Swedish firm, a provider of automated micro-immunoassays for therapeutic protein development, cites Merck & Co, GlaxoSmithKline and Pfizer among the customers for its Gyrolab analytical platform. The fundraising was led by SLS Invest, the company's leading shareholder with an 88% stake in Gyros.

Medinco CFM, an Italian API producer, has bought a manufacturing plant near Mulhuddart, Ireland, from the privately held **Helsinn** group of Switzerland. The cGMP-compliant plant employs 31 people and will continue to produce APIs for Medinco CFM. The new owner has manufacturing subsidiaries in northern Italy and also owns two distribution companies – one in Italy and one in Spain.

Bioniche Life Sciences has said that it will miss the deadline to address its short-term liquidity concerns before its credit facility matures. The Canadian firm has employed several initiatives over the past two months to handle its liquidity issues and extended the maturity date of its secured revolving credit facility with the investment group Valens US until June 30th.

Orexo may look to acquire sales teams to build its own force in order to sell its opioid addiction therapy **OX219**, which it acquired when it bought PharmaKodex in February, the company's CEO Torbjorn Bjerke said at a recent Piper Jaffray Europe conference held in London. Most of the Swedish pharmaceutical company's other lead products are sold by its partners.

Teva Pharmaceutical Industries is to exercise its option to complete a $13.5 million investment in **Andromeda Biotech** in return for the worldwide marketing rights to DiaPep277 for the treatment of type 1 diabetes. The Israeli subsidiary of Clal Biotechnology signed the original agreement with Teva in 2008.

Neovacs is set to expand clinical testing of TNF-alpha kinoid to include rheumatoid arthritis patients following positive preliminary findings from a Phase I/II study in Crohn's disease patients. With all the initial dose groups having received the product, no significant adverse reactions have been detected in the ongoing study. In addition, it does not appear to induce cell-mediated immunity, "meaning patients are not permanently immunised against TNF-alpha", the company's chief executive Guy-Charles Fanneau de La Horie said.

A medical centre in **Taiwan** is to help **Neuralstem** prepare for a local clinical trial with its human spinal cord-derived neural stem cells for the treatment of stroke. The sponsored preclinical research programme will take up to a year, the US firm said. The aim is to clear the way for a trial to assess the cell therapy in patients whose post-ischaemic stroke symptoms have stopped improving more than six months after the event.

This is a round up of Scrip's business news. Read the full stories plus others at scripnews.com

US FDA wants more data on Lundbeck's Serdolect

The US FDA has issued Lundbeck a complete response letter for its atypical antipsychotic Serdolect (sertindole) for the treatment of schizophrenia.

According to Lundbeck, the agency requested additional data to "best understand the appropriate patient population for which Serdolect could be made available".

Serdolect's user fee date was originally set for May 15th. This passed without action, indicating that the product's US approval may be troubled. The drug was also subject to scrutiny by an FDA advisory panel last month over its cardiac safety profile.

The panel concluded that Serdolect could be safely used by some schizophrenia patients but was not safe for broad treatment owing to its association with cardiac arrhythmias and sudden death linked to QT interval prolongation (scripnews.com, April 8th, 2009).

The experts recommended reserving sertindole for highly refractory patients, and they were optimistic that individuals at heightened risk for cardiac events could be identified in advance. Baseline and regular EKG monitoring was suggested, although some advisors doubted its usefulness in identifying patients at risk.

In response to these concerns, Lundbeck proposed a risk minimisation plan – although not a formal REMS – to address the cardiac risk.

The measures include a "black box" warning on QT prolongation, a contraindication for patients with known cardiac risk factors, and a monitoring of safety signals through drug utilisation and outcomes databases.

relaunch

The antipsychotic was initially launched in Europe in 1996, but marketing was suspended two years later because of its cardiac safety issues. The drug was relaunched in the EU in 2006 after Lundbeck submitted additional data from 6,000 patients showing no increased mortality risk.

Serdolect is an antagonist of dopamine D_2, serotonin $5HT_2$ and $5HT_6$ receptors as well as alpha 1 adrenoceptors. According to the company, the drug has high limbic selectivity, resulting in a low propensity for extrapyramidal symptoms.

It is also devoid of anticholinergic and antihistamine activity – action on these could be associated with cognitive and sedative side-effects.

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IS Pharma launches Variquel in the UK

IS Pharma has launched Variquel (terlipressin) for the treatment of bleeding oesophageal varices in the UK. The synthetic vasopressin analogue, which gained approval under the EU's mutual recognition procedure in March, is already marketed for this indication in Germany, Austria and Switzerland. Five vials of the product, for five injections, will cost £89.48. Terlipressin is under regulatory review, as Orphan Therapeutic's Lucassin, in the US as a treatment for type 1 hepatorenal syndrome (scripnews.com, June 16th, 2009).

First advanced therapy, ChondroCelect, OKd in EU

A cell-based medicine for repairing knee damage has become the first product to be recommended for approval by the European Medicines Agency under the EU's new advanced therapy regulatory framework.

ChondroCelect, which is produced by the Belgian biomedical company TiGenix, is used to repair defects in the cartilage of the femoral condyle (the end of the thighbone) in the knee. It consists of chondrocytes taken from a healthy region of the patient's cartilage that are grown outside the body and then reinserted during surgery.

According to the EMEA, ChondroCelect allows single symptomatic cartilage defects to be repaired and functional cartilage restored, with the aim of reducing the risk of osteoarthritis of the knee over the longer term. The therapy has some possible side-effects, including arthralgia, cartilage hypertrophy, and joint crepitation and swelling.

Under the regulatory framework for advanced therapy medicinal products (ATMPs), products based on gene and somatic cell therapy and tissue engineering can be evaluated by the EMEA's new Committee for Advanced Therapies (CAT). The CAT's opinion is then confirmed by the agency's main scientific committee, the CHMP.

ChondroCelect is the first product to be given a positive opinion under this new system. The opinion now has to be turned into a centralised EU marketing authorisation by the European Commission, a process that normally takes two to three months.

The product was originally submitted for approval in mid-2007, based on a 118-patient study comparing it with the current standard treatment, microfracture (scripnews.com, March 6th, 2007). It found that structural repair at 12 months was better with ChondroCelect, and there was also a slight improvement in clinical outcome (symptom relief and improvement in overall function and quality of life) at 12 and 18 months using the KOOS (knee injury and osteoarthritis outcome score).

However, the EMEA evaluation process was held up when the company had to answer some questions raised by the agency towards the end of 2008. As part of the approval process, TiGenix must submit a risk management plan for ChondroCelect with a series of measures including further studies to ensure that safety and efficacy are "robustly" followed up once the product is launched.

Once EU approval has been granted, the product will be launched gradually in Europe, starting probably with Germany, the UK and France, said spokesman Kris Motmans. The EU data will also be used in seeking approval of the product in the US, he added.

Analysts at Piper Jaffray say reimbursement negotiations, which will be critical to the product's success, should be significantly strengthened by data from 36-month analysis of the clinical study.

Wilfried Dalemans, head of regulatory affairs at TiGenix, said obtaining regulatory approval of the first ATMP product in Europe "shows that advanced cell therapy products can be developed according to the medicinal product regulatory requirements".

TiGenix recently raised €5.4 million to set up a new Dutch facility for the commercial production of its cell-based products.

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EU wants to withdraw all dextropropoxyphene products

All marketing authorisations for dextropropoxyphene-containing products should be withdrawn in the EU because of the risk of intentional or accidental overdose, the EU's CHMP has recommended. The risk of overdosing only became evident when data from national poison centres and mortality statistics throughout the EU were analysed in depth, the committee adds.

The withdrawal should include products containing dextropropoxyphene alone and those where it is combined with paracetamol, the committee said. The recommendation will now be forwarded to the European Commission to give a legally binding decision. The products are expected to be withdrawn gradually to allow patients to be transferred onto alternative therapies.

The UK withdrew the marketing authorisation for dextropropoxyphene combined with paracetamol (which is called co-proxamol in the UK) in 2005, and last week a published analysis showed that this had been associated with a decline in accidental or intentional overdoses in the following two years in the UK, without an increase in fatalities associated with other products remaining on the market.

Dextropropoxyphene has been available in the EU for about 40 years, but safety reviews in different countries have led to different conclusions, the EMEA notes. Sweden withdrew authorisations for co-proxamol in 2005, while co-proxamol (sometimes with caffeine) products are authorised in Belgium, Cyprus, France, Luxembourg, Malta and Portugal, and in the non-EU country Norway. Products containing dextropropoxyphene alone are authorised in 10 EU countries – Belgium, Denmark, Finland, France, Greece, Italy, Luxembourg, the Netherlands, Spain and Sweden.

In the US, where dextropropyoxyphene is known as propoxyphene, an FDA advisory panel narrowly voted earlier this year that propoxyphene-containing products (such as Xanodyne's Darvocet, Darvon and generics) should be removed from the market. However, there were concerns that alternative analgesics also carry a risk of dependence and abuse, and have not been scrutinised to the same level as propoxyphene. In addition, propoxyphene is usually formulated with a less soluble salt in the US than in the UK, and is prescription only. More recently, Public Citizen sued the FDA for failing to withdraw propoxyphene.

In the EU, analysis of dextropropoxyphene plus paracetamol's risks and benefits started in November 2007, a review which was widened in March this year to include dextropropoxyphene marketed alone. Initially, the review looked at data submitted by marketing companies and those in the published literature. However, it was only when data from poison centres, coroners' services, hospital statistics, national mortality statistics and toxicology services were analysed that the actual risk of dextropropoxyphene-containing medicines became apparent, the CHMP says.

The review also concluded that dextropropoxyphene was only a weak analgesic, and that co-proxamol was no more effective than paracetamol or ibuprofen alone in short-term pain. In long-term pain, there was no evidence that co-proxamol was more effective than alternative analgesics, the CHMP said.

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Simponi and Cimzia get positive opinions

Two competing anti-TNF therapies, Centocor (J&J) and Schering-Plough's Simponi (golimumab) and UCB's Cimzia (certolizumab pegol), have received positive endorsements for approval from the CHMP.

Simponi, a fully humanised anti-TNF, has been recommended for the treatment of moderate-to-severe rheumatoid arthritis, in combination with methotrexate in patients who have previously had an inadequate response to disease-modifying therapy; active psoriatic arthritis, alone or in combination with methotrexate in patients who have had an inadequate response to disease-modifying therapy; and active ankylosing spondylitis in patients who have had an inadequate response to conventional therapy. Meanwhile, Cimzia is set to become the first pegylated anti-TNF inhibitor for the treatment of RA, in combination with methotrexate, or alone in the case of methotrexate intolerance, where response to disease-modifying drugs has been inadequate. The pegylation extends the drug's half-life and enables dosing every two or four weeks. The drug will be available in a pre-filled syringe, which is suitable for self-administration. Cimzia was launched in the US and Switzerland for the treatment of Crohn's disease last year and subsequently gained an approval for RA in May.

Simponi will be dosed monthly at 50mg, and will be available in a SmartJect autoinjector, as well as in a prefilled syringe. Simponi received its first approval in the US in April for RA.

The drugs will be competing with four other subcutaneous treatments for RA on the European market or soon to be launched. Amgen/Wyeth's Enbrel (etanercept) – a TNF-blocker administered weekly and approved for RA – including early-stage disease and polyarticular course juvinaile RA; J&J's Remicade (infliximab) – a chimaeric antibody against TNF-alpha given by intravenous infusions every six to eight weeks in patients with both early and late stage RA; Abbott's Humira (adalimumab) – a monoclonal antibody anti-TNF given fortnightly given to patients with RA and juvenile RA; and Roche's Actemra (tocilizumab) – a recombinant humanised monoclonal antibody against the interleukin-6 receptor, given every four weeks, which received an EU approval for RA in January, but is not yet launched.

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BMS's Onglyza gets first nod for diabetes in EU

The CHMP has adopted a positive opinion on Bristol-Myers Squibb/AstraZeneca's Onglyza (saxagliptin) for type 2 diabetes as an add-on combination therapy to metformin, a thiazolidinedione, or a sulphonylurea.

Onglyza is an orally available dipeptidyl peptidase IV (DPP-IV) inhibitor. DPP-IV inhibitors reduce the degradation of glucagon-like peptide 1 (GLP-1; a hormone produced in response to food intake), which results in increased insulin secretion.

Onglyza has been filed for approval in both the EU and the US. Merck & Co's Januvia (sitagliptin), which was the first-in-class DPP-IV inhibitor, is already approved in the US and in the EU. Novartis's DPP-IV inhibitor Galvus (vildagliptin) is available in the EU, but not in the US. Takeda's alogliptin had also been filed in the US, but the product received a complete response letter on June 26th (see story on page 18). Phenomix's dutogliptin and Boehringer Ingelheim's linagliptin are in Phase III development. Onglyza's EU filing was based on the results of six main Phase III trials involving more than 4,000 subjects. These examined the drug as initial therapy (alone and in combination with metformin) and as add-on therapy in patients who failed to achieve glycaemic control on metformin, a thiazolidinedione or a sulfonylurea.

Most common side-effects included upper respiratory infection, urinary tract infection and gastroenteritis. Incidence of hypoglycaemia was low, but increased when Onglyza was taken with a sulfonylurea. The incidence of oedema is low but may increase when taking the drug with a thiazolidinedione, the CHMP said.

Earlier this year, the FDA extended the PDUFA date for Onglyza to July 30th. The companies said only that the agency needed more time to review the submission. A panel of FDA's outside experts also reviewed saxagliptin's heart safety and concluded that it posed no unacceptable cardiovascular risk.

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Vinflunine receives EU positive opinion in bladder cancer

Pierre Fabre's new vinca alkaloid anticancer, Javlor (vinflunine ditartrate, 25mg/ml), has received a positive opinion from the EU's CHMP, for the second-line treatment of transitional cell carcinoma of the urothelium.

Vinflunine, a new chemical entity, is expected to be indicated as a "monotherapy for the treatment of adult patients with advanced or metastatic transitional cell carcinoma of the urothelial tract after failure of a prior platinum-containing regimen", the CHMP says. It is administered by infusion.

The product was licensed to Bristol-Myers Squibb for development in the US, Japan and other markets, but the rights were returned to Pierre Fabre in 2007 after BMS revealed that it did not expect to file an NDA in the US for the treatment of bladder cancer following talks with the FDA. Pierre Fabre already markets a vinca alkaloid anticancer, Navelbine (vinorelbine).

A clinical trial showed the benefits of vinflunine in patients compared with best standard of care alone, the CHMP reports. The most common side-effects included abdominal pain, nausea, vomiting, constipation, diarrhoea, and inflammation of the mucosa of the mouth. Vinflunine, like other vinca alkaloids, interacts with cellular tubulin, preventing chromosomal segregation during cell division and inducing cell death through apoptosis.

Phase III trials are ongoing in other indictions.

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Salvacyl launched in EU for sexual deviancy

DebioPharm has launched its gonadotropin releasing hormone (GnRH) agonist analogue Salvacyl (extended-release triptorelin), for the treatment of sexual deviancy by the reversible reduction of serum testosterone to castrate levels, in Germany and Belgium.

"We can now offer people suffering from this controversial disorder an alternative and a complementary treatment to surgical and currently used chemical castrations, as well as to other types of medication," said Rolland-Yves Mauvernay, founder and president of DebioPharm.

Salvacyl is registered in seven other European countries – France, the UK, Sweden, Norway, Denmark, the Netherlands and Finland – and will be launched progressively by DebioPharm's commercial partners throughout 2009 and 2010.

Tripotorelin has been available under the trade name Decapeptyl for the treatment of locally advanced or metastatic hormone-dependent prostate cancer. Salvacyl is dosed the same as Decapeptyl, and will therefore be priced comparatively.

"The name has been changed in order to clearly separate the two products and to avoid the patient confusion that might arise from any negative connotations that Salvacyl may carry," the company said.

It stressed that Salvacyl alone would not provide a cure to deviant sexual behaviour (also known as paraphilia), as patients would also require psychotherapy, but it "would provide the community with an additional tool".

The company said that for the treatment of sexual deviation in men, administration of Salvacyl every three months is an advantage over daily oral forms or intramuscular weekly injections with anti-androgens such as cyproterone acetate (CPA) and medroxyprogesterone acetate (MPA). Salvacyl is also expected to be associated with fewer side-effects than CPA and MPA, with a reduced risk of hepatocellular damage, thromboembolism and gynaecomastia.

DebioPharm did not conduct any clinical trials to prove that castration with Salvacyl diminishes sexual deviancy; it used a trial published in the *New England Journal of Medicine* in 1998 to support its premise. In the uncontrolled observational study, 30 men with severe long-standing paraphilia received monthly injections of 3.75mg of triptorelin and supportive psychotherapy for eight to 42 months. The efficacy of the therapy was evaluated monthly by the intensity of sexual desire and symptoms scale, and yearly by the three main complaints questionnaire which monitored the decrease in the three main problems that the patient nominates he is suffering from.

All of the men had a decrease in the number of sexual fantasies and desires, from a mean of 48 per week before therapy to zero during therapy ($p<0.001$), and a decrease in the number of incidents of abnormal sexual behaviour, from a mean of five incidents per month to zero ($p<0.001$). The results of the three main complaints questionnaire also improved with triptorelin therapy. Six men stopped treatment after eight to 10 months, including three who wanted to become fertile. In the five men in whom follow-up was possible, two men resumed treatment, with good results. However, three men who stopped triptorelin because of side-effects and were subsequently given 200mg/day of CPA did not control their paraphilia, resulting in two patients being sentenced for sex crimes.

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River Plate/Alcon's dry eye treatment needs more study, US panel says

The efficacy of River Plate Biotechnology/Alcon's dry eye treatment Rejena (sodium hyaluronate ophthalmic solution, 0.18%) requires further study before approval, the US FDA's dermatologic and ophthalmic drugs advisory panel has recommended.

In a six to one vote, the panel said adequate efficacy and safety had not been demonstrated. The advisors concluded that River Plate could not rely upon the efficacy results of a published 2005 French study because the trial failed its primary endpoints and used saline, rather than vehicle, as a comparator, clouding the drug's true efficacy. Although a second randomised trial, RP-001, conducted by River Plate showed marginal statistical significance of sodium hyaluronate against vehicle, the results were not sufficiently robust to justify approval on that basis alone, panellists said.

"I wasn't overly impressed with the efficacy of the drug compared to vehicle, albeit there were measures bordering clinical significance," said panel chairman Dr Michael Repka of Johns Hopkins Hospital in Baltimore, Maryland.

The experts recommended River Plate conduct another trial similar to the RP-001 study, but said that the company should also establish that there is no interaction between sodium hyaluronate and the usefulness of lissamine green staining to assess eye damage. Change from baseline in lissamine green staining was one of two primary efficacy endpoints in the 001 trial.

Rejena contains a highly purified specific fraction of sodium hyaluronate derived by fermentation from bacteria. The formulation is marketed in 27 countries in Europe and Asia as a viscoelastic lubricant eye drop under the brand names Vismed, Vislube and Hylovis. Alcon licensed US rights to the dry eye treatment in 2007. River Plate, a subsidiary of Lantibio, submitted the NDA in January. Sodium hyaluronate currently is regulated as a class 3 medical device in the US. The FDA considers the compound to be a new molecular entity because it has never been approved as a drug product. However, it is listed as an inactive ingredient in over-the-counter products intended to lubricate the eyes.

If approved, Rejena would be the first prescription drug in the US specifically indicated for the treatment of signs and symptoms of dry eye disease. Allergan's Restasis (cyclosporine ophthalmic emulsion) 0.05% is approved to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis. There are also numerous OTC demulcent products that manage symptoms of dry eye disease.

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Meeting

The EDQM is holding a conference on ***Herbal Drugs and Herbal Drug Preparations*** in Vienna, Austria, on September 25th. For further details, visit www.edqm.eu.

***Scrip*'s Pipeline Watch, now published weekly, brings you the most recently reported late-stage clinical trial and regulatory developments from the more than 10,000 drugs candidates currently under active research worldwide, in an easily digestible table format.**

Late-stage clinical developments for the week June 17th-23rd, 2009

Compound	Company	Indication	Mechanism of action/activity	Development status	Comments
Musculoskeletal					
Celebrex (celecoxib)	Pfizer	lumbago	cyclooxygenase 2 inhibitor	additional approval	Japan
Celebrex	Pfizer	scapulohumeral periarthritis	cyclooxygenase 2 inhibitor	additional approval	Japan
Celebrex	Pfizer	cervico-omo-brachial syndrome	cyclooxygenase 2 inhibitor	additional approval	Japan
Celebrex	Pfizer	tendinitis	cyclooxygenase 2 inhibitor	additional approval	Japan
Celebrex	Pfizer	tendosynovitis	cyclooxygenase 2 inhibitor	additional approval	Japan
Dysport	Ipsen	cervical dystonia	acetylcholine release inhibitor	additional launch	US
Dysport	Medicis	glabellar lines	acetylcholine release inhibitor	additional launch	US; licensed from Ipsen
Pennsaid) (diclofenac)	Nuvo Research	osteoarthritis	cyclooxygenase 1 inhibitor	new licensee	Mallinckrodt (Covidien); US
Nervous system					
Pristiq (desvenlafaxine)	Wyeth	fibromyalgia	5 hydroxytryptamine uptake inhibitor	discontinued	
Vabicaserin (sustained-release)	Wyeth	schizophrenia	5 hydroxytryptamine 2C agonist	discontinued	
LPCN-1050	Lipocine	bipolar psychosis	unidentified	Phase II initiated	
LPCN-1050	Lipocine	migraine	unidentified	Phase II initiated	

Source: Citeline Drug Intelligence

GSK's anti-emetic Rezonic draws FDA complete response

The US FDA has issued a complete response letter for GlaxoSmithKline's investigational anti-emetic Rezonic (casopitant mesylate).

The company said it was reviewing the letter and would talk to the agency to determine the next steps. GSK did not specify what issues were raised or whether additional clinical data would be needed for approval.

The NDA has been with the agency for more than a year, making it long overdue for regulatory action. It was filed on May 29th, 2008, for use in combination with other anti-emetics to prevent chemotherapy-induced nausea and vomiting and post-operative nausea and vomiting. The FDA cancelled an advisory panel review originally scheduled for last month.

Casopitant is a neurokinin NK-1 receptor antagonist, the same class as Merck & Co's Emend (aprepitant). The NDA sought approval for oral and iv formulations.

Two pivotal Phase III trials tested Rezonic in combination with GSK's $5HT_3$ receptor antagonist Zofran (ondansetron) and dexamethasone

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Pixantrone's US filing completed for NHL

Cell Therapeutics has completed its NDA filing with the US FDA for its experimental chemotherapy drug pixantrone to treat relapsed or refractory aggressive non-Hodgkin's lymphoma (NHL). The company requested a priority review for the product, which is available in Europe on a named-patient basis. Pixantrone, an anthracenedione was designed to reduce the potential for heart damage compared with currently available anthracyclines (such as doxorubicin) and other anthracenediones (such as mitoxantrone) without a loss in antitumour activity.

The filing is based on the pivotal Phase III EXTEND trial in which 140 patients with aggressive NHL who had failed on prior regimens were randomised to receive either pixantrone or another standard single-agent drug, selected by the physician, which may have been Roche/Genentech's rituximab or one of several (non-anthracycline) chemotherapies such as oxaliplatin, gemcitabine, mitoxantrone or VP-16. Most patients had failed three prior regimens including R-CHOP, which contains the anthracycline doxorubicin.

The primary endpoint was complete remission rate (confirmed or unconfirmed CR). 20% of patients on pixantrone achieved this, compared with 5.7% for the standard chemotherapy arm. No patient in the control arm achieved a confirmed CR, compared with 11% who received pixantrone. Additionally, pixantrone had a significant improvement in median progression-free survival (PFS) – 4.7 months vs 2.6 months.

Although the grade 3/4 cardiac disorder rate was the same among the two treatment groups (1.5%), there was a slightly higher incidence of serious cardiac disorders in patients treated with pixantrone (8.8% vs. 4.5%). Cell Therapeutics' CEO Dr James Bianco told *Scrip* that the rate seen with pixantrone was much lower than would typically be seen with a standard anthracycline, while the efficacy of this class of drug was retained.

The company hopes to show this in another Phase II/III trial in patients with newly diagnosed aggressive NHL in which pixantrone is being pitted directly against doxorubicin (R-CPOP versus R-CHOP). The primary non-inferiority endpoint is complete remission, and so it will not likely be accepted by the FDA to register pixantrone for first-line use, Dr Bianco added.

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Cardiovascular safety study needed for alogliptin

The US FDA has confirmed that Takeda will need to perform an additional cardiovascular safety study for its NDA on the DPP-4 inhibitor alogliptin. The request came as the agency issued a complete response letter on June 26th, the product's user fee date, and followed discussions between the two parties. "The FDA has asked Takeda to conduct an additional cardiovascular safety trial that satisfies the December 2008 FDA guidance," Takeda said.

The FDA indicated in March that its new guidelines on cardiovascular risk for type 2 diabetes drugs would apply to alogliptin, despite the product being filed a year earlier than these, in December 2007. This was because of what it said were insufficient data to meet the statistical requirements of the guidance (scripnews.com, March 6th, 2009).

Alogliptin missed its original user fee date in October last year because the FDA needed more time to complete its review. The new formal requirement for an additional study could mean a delay of at least two years to the US approval of alogliptin. This means the drug is now unlikely to be approved in time for the 2011 loss of US exclusivity for Takeda's current mainstay antidiabetic, Actos (pioglitazone).

Investors had largely anticipated the delay, although the news still weighed on Takeda's share price, which fell by around 2% in Tokyo on June 29th, the first trading day following the complete response letter.

Alogliptin is also facing a delay in Europe, where a filing is now expected sometime in 2012 to give time for an additional long-term clinical study (scripnews.com, June 5th, 2009). A submission was made last October in Japan, which could end up being alogliptin's first market.

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US FDA approves first generic Plan B

Watson Pharmaceuticals will be the first company in the US to market a generic version of Teva Pharmaceutical Industries' emergency contraceptive Plan B (levonorgestrel) tablets 0.75mg, after it won approval of its ANDA.

For now, Watson's generic levonorgestrel will be available by prescription only for women aged 17 years and younger. Teva has exclusive rights to an over-the-counter version of the product for women aged 18 and older until August 24th, the FDA said.

Plan B has been available OTC to women aged 18 years and older since 2006. It was first approved in 1999, for prescription use only, for women in all ages. The FDA said in April that it would provide no objections to a judge's order to allow the OTC sales to 17-year olds, despite an earlier stance on broadening access.

Watson plans to launch its generic as Next Choice shortly.

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PriCara, a subsidiary of Johnson & Johnson, has launched its analgesic **Nucynta** (tapentadol) CII immediate-release tablets in the US for the treatment of moderate-to-severe pain in adults. The drug is available in 50mg, 75mg and 100mg tablets. "In clinical trials, Nucynta provided patients with effective pain relief and was shown to have fewer side-effects often reported with prescription pain medications that act on the mu-opioid receptors," said Dr Perry Fine, of the University of Utah and consultant to PriCara.

The US FDA has approved **Kowa Pharmaceuticals America**'s **Cambia** (diclofenac with potassium bicarbonate) for the treatment of acute migraine with or without aura in adults. The company expects to launch Cambia in the fourth quarter of 2009. Cambia is an immediate-release powdered oral-formulation of the NSAID diclofenac potassium.

Ista Pharmaceuticals' **Bepreve** (bepotastine besilate ophthalmic solution, 1.5%) is safe and effective for treating ocular itching associated with allergic conjunctivitis, the US FDA's outside advisors have said. In a non-controversial review that lasted only two hours, the dermatologic and ophthalmic drugs advisory panel endorsed bepotastine by a seven to zero vote. The NDA was filed last November and has a September 12th user fee date.

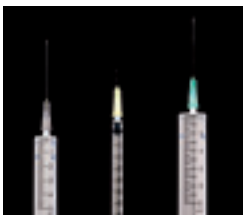
Acura Pharmaceuticals has received a preliminary communication from the US FDA on the NDA of its abuse-deterring analgesic, **Acurox** (oxycodone plus niacin), which resulted in the drug missing its June 30th PDUFA date. Acura's share price tumbled by 22% on the news, closing at $5.89 on Nasdaq on June 23rd. According to the company, the FDA's comments are still subject to change.

Cephalon's new experimental multi-targeted kinase inhibitor, **lestaurtinib** (CEP-701), has failed to show a benefit in a pivotal trial in patients with relapsed acute myelogenous leukaemia (AML) expressing FLT3 activating mutations, but experts remained hopeful about the strategy of inhibiting FLT3 in AML. The failed trial enrolled 224 AML patients in their first relapse following standard induction chemotherapy.

Forest has released positive top-line data of its injectable antibiotic **ceftaroline** from two pivotal Phase III clinical trials, FOCUS I and FOCUS II, which demonstrate its non-inferiority to ceftriaxone for the treatment of community-acquired bacterial pneumonia requiring hospitalisation. Ceftaroline is a bactericidal broad-spectrum cephalosporin antibiotic in development by the company for the treatment of Gram-positive pathogens such as MRSA and multidrug-resistant *Streptococcus pneumoniae*, as well as common Gram-negative micro-organisms.

Jazz Pharmaceuticals' second Phase III trial of **Xyrem** (sodium oxybate) for fibromyalgia has met its primary endpoint, according to top-line results. The findings match previously reported full results from a US-based Phase III trial. Jazz's shares leapt by 38% on these data on Nasdaq on June 25th.

Glenmark's oral DPP IV inhibitor for type 2 diabetes, **melogliptin**, is expected to enter Phase III studies by the end of the year. The compound recently completed a 12-week Phase IIb trial in 494 patients with type 2 diabetes and demonstrated improved glycaemic control in these patients, besides an "excellent" safety and tolerability profile. In addition, patients taking melogliptin experienced a low incidence of hypoglycemia and neutral effect on body weight.



Diamyd has started a Phase II trial to examine whether the company's experimental vaccine, its lead candidate, which is also called Diamyd, is effective as a prophylactic treatment for children at high risk of developing diabetes. Diamyd is also in two Phase III trials in patients newly diagnosed with type 1 diabetes, an indication for which the Swedish company plans to submit an NDA in 2011.

Sanofi-Aventis has launched its fast-acting insulin analogue **Apidra** (insulin glulisine) in Japan, for the management of prandial glycaemic levels in adults with diabetes mellitus. The recombinant product is administered around meal times for the short-term control of blood sugar levels, and can be used with the SoloSTAR pen delivery system. Together with a 300 unit cartridge, this is reimbursed at ¥2,237 ($23.50) per kit, with a cartridge reimbursed at ¥1,596 and a 100 unit/ml vial for injection at ¥380.

Menarini and **Oscient Pharmaceuticals** have withdrawn the EU marketing application of quinolone antibacterial **Factive** (gemifloxacin) 320mg film-coated tablets for the treatment of community-acquired pneumonia, acute bacterial exacerbations of chronic bronchitis and acute bacterial sinusitis. In its official letter, Menarini stated that the withdrawal was based on the CHMP's view that the data provided did not allow the committee to conclude on a positive benefit-risk balance for Factive at that time.

UCB is making available again its transdermal patch, **Neupro** (rotigotine), in the EU, following approval by the European Commission of last month's positive opinion from the CHMP. It is indicated for the treatment of Parkinson's disease and a new indication, restless legs syndrome. Since last year, supplies of Neupro have been restricted because of the formation of crystals within the patches.

Santhera Pharmaceuticals is to collaborate with Columbia University in New York to investigate **Catena** (idebenone) in a Phase II study as a treatment of MELAS (mitochondrial encephalopathy, lactic acidosis and stroke-like episodes). Separately, Santhera is also set to collaborate with the US National Institutes of Health (NIH) to investigate Catena as a potential treatment of primary progressive multiple sclerosis.

There has been some positive news for **Takeda**'s late-stage pipeline with the start of Phase III hypertension trials in Japan for the company's candesartan successor, **azilsartan** (TAK-536). The angiotensin II antagonist, in Phase II development in the US and Europe, will be key to limiting the impact of the loss of patents for candesartan around the 2012 period.

Boehringer Ingelheim and local partner **Astellas** have launched a combination of telmisartan and the diuretic hydrochlorothiazide in Japan, as **Micombi**, to treat hypertension. The product is a single once-daily tablet containing either 40mg or 80mg of the angiotensin II antagonist with 12.5mg of HCTZ.

This is a round up of Scrip's R&D news. Read the full stories plus others at scripnews.com

US FTC head makes economic case against "reverse payment" deals

Eliminating "reverse payment" patent settlements between innovators and generics firms would save US consumers about $3.5 billion a year, one third of which would accrue to the federal government, US Federal Trade Commission (FTC) chairman Jon Leibowitz said in a speech to the Center for American Progress.

In making an economic case for banning patent settlement agreements whereby a generic company receives money or some other remuneration from an innovator to delay generic entry, Mr Leibowitz said the resulting savings could be used to help fund healthcare reform.

"From my perspective ... the decision about whether to restrict pay-for-delay settlements should be simple," said Mr Leibowitz, a long-time opponent of such pacts. "On the one hand you have savings to American consumers of $35 billion or more over 10 years – about $12 billion of which would be savings to the federal government – and the prospect of helping to pay for healthcare reform as well as the ability to set a clear national standard to stop anticompetitive conduct. On the other hand you have a permissive legal regime that allows competitors to make collusive deals on the backs of consumers."

The dollar savings arguments could help nudge the latest versions of settlement-banning legislation through Congress as part of healthcare reform. Standalone reverse payment bills are currently under consideration in House and Senate committees. However, Democratic lawmakers struggling to find ways to pay for healthcare reform estimated to cost more than a $1 trillion are eager to extract cost-savings wherever they can find them, and it is possible that a reverse payment settlement ban could end up in a broader overhaul package.

The FTC's cost-savings projections were based on an analysis of all Hatch-Waxman patent settlements filed with the agency between 2004 and 2008. Data showed that of all settlements resulting from a paragraph IV challenge, approximately 24% included both restrictions on the timing of generic entry and a payment to the generic firm. On average, agreements with payments allowed generic entry 17 months later than those without payments. The FTC's estimates assume that the rate of settlements with payments, as well as the average length of delay in generic entry, will remain the same. The calculations exclude injectable drugs.

"These numbers were based on pretty conservative assumptions," Mr Leibowitz said. "Perfectly reasonable alternative assumptions would lead you to $75 billion in savings for consumers, which would work out to $25 billion for federal programmes, over the next decade."

The innovator and generics industries have opposed efforts to ban reverse payment deals, asserting they have a right to enter into settlements within the confines of the patent under dispute. However, Mr Leibowitz scoffed at the drug industry's arguments about potential negative ramifications if such settlements are barred.

"Brand companies ... claim that barring pay-for-delay settlements would mean less innovation. If anything, however, brand companies are most likely to pay off a generic competitor when they have not innovated. As defenders of these settlements have conceded, the incentive to pay a generic to abandon its patent challenge is greatest for the weakest patents."

Some generics firms suggest that banning reverse payment settlements will result in fewer patent challenges. "I have seen no evidence to support this argument," Mr Leibowitz countered. "In any event, if generics are filing patent challenges only to get a payoff, then those patent challenges are no longer serving consumers."

The FTC has had a difficult time challenging the practice in court, where appellate judges have rebuffed its arguments in several cases. To date, the Supreme Court has refused to weigh in on the issue. On June 22nd the high court declined to hear a lawsuit brought by independent purchasers of Bayer's antibiotic Cipro (ciprofloxacin) who challenged a 1997 patent settlement with Barr Pharmaceuticals. The FTC had submitted an amicus brief in the appeals court supporting the plaintiffs' argument.

Nevertheless, the FTC has continued to file lawsuits in carefully selected cases, including complaints against Cephalon over reverse payment settlements for the narcolepsy drug Provigil (modafinil) and Solvay for deals involving its Androgel testosterone product. Mr Leibowitz said the odds for enacting legislation are improving. Earlier this month the House energy and commerce panel's subcommittee on commerce, trade and consumer protection approved the Protecting Consumer Access to Generic Drugs Act by a 16-10 vote. The measure would prohibit patent settlement agreements in which an ANDA filer receives anything of value and agrees not to manufacture or market its generic. The Senate judiciary committee is considering a similar measure.

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US boosts pandemic flu funding

US President Barack Obama has signed a supplemental appropriations bill that includes $7.7 billion in influenza pandemic preparedness funding. The figure far exceeds the $2 billion allocation originally passed by the House in mid-May to respond to the H1N1 flu outbreak.

In April, Mr Obama had originally sought $1.5 billion in supplemental funding for the current fiscal year to combat the H1N1 flu. In early June he asked the House for $2 billion in emergency appropriations on top of his original request. The original Senate-passed measure included $1.5 billion in funding.

The final bill was negotiated by lawmakers from both chambers. It provides $7.3 billion for the HHS and the CDC. $1.5 billion of this amount is immediately available, and $5.8 billion is classified as contingent emergency appropriations. The funds will be used to develop, purchase and administer vaccines, replenish and expand federal and state antiviral stockpiles, and expand domestic and global disease detection and surveillance efforts.

The contingent monies can only be used if the president provides written notice to Congress that emergency funds are required to address critical needs related to emerging influenza viruses.

$350 million will go to assist state and local governments prepare for and respond to a pandemic. The US Agency for International Development will receive $50 million to assist foreign countries to develop detection capacity, respond to outbreaks and implement vaccination programmes.

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Authorised generics could benefit consumers, US FTC finds

Competition from authorised generics during an ANDA first-filers' 180-day exclusivity period reduces drug prices, but consumers are harmed when innovators agree not to launch an authorised generic as part of a "reverse payment" patent settlement that also delays the first generic's entry, a US Federal Trade Commission (FTC) report found.

The presence of an authorised generic reduces the first-filer's revenues during the six-month exclusivity period by about half, and this potential loss makes it more appealing for generics firms to enter into reverse payment settlements with innovators, the FTC said in an interim report on the short-term competitive effects of authorised generics. The document does not reach conclusions about the net impact on consumers and the economy, and analysis of the long-term impacts will be part of the final report, although it is uncertain when this will be released.

The interim report's conclusions suggest that arguments asserting consumers are financially harmed in the short-term by the entry of authorised generics will not succeed in advancing legislation to ban such products. Instead, proponents of this type of legislation will have to wait to see if the FTC's full analysis of authorised generics' long-term effects demonstrates that generics companies have less incentive to challenge patents and file ANDAs, resulting in less competition to brand drugs.

However, the report's statement that "consumers benefit and the healthcare system saves money during the 180-day exclusivity period when an authorised generic enters the market" may discourage House and Senate lawmakers from moving to ban the entry of authorised generics at this time given their current intensive focus on developing healthcare reform legislation that reduces costs to consumers and the federal government.

The interim report presents the first set of results from a study undertaken by the FTC, at the request of various lawmakers, on the effects of authorised generics on competition. The commission subpoenaed almost 200 innovator, generic and authorised generic firms in 2007 seeking information on authorised products launched after January 2001, all related brand and ANDA drugs, sales and pricing data and other documents.

The presence of an authorised generic during the 180-day exclusivity period reduces retail prices by an average of 4.2% more, relative to brand price prior to any generic competition, than when only the first-filed ANDA is on the market, the FTC found. Authorised generics appear to have a larger impact on discounts in product markets with high sales. On average, wholesale prices are 6.5% lower in the face of an authorised generic.

However, the authorised generic's revenue impact on the first-filer company is significantly greater, with an estimated average decline of 47-51% during the exclusivity period. "The impact of authorised generic entry likely changes the calculus of business decision-making for both the generic and brand firms," the FTC report said, adding that these impacts will be further explored in the final study.

The report also looks at the inclusion of authorised generics provisions in patent settlement agreements, a practice that has grown in recent years.

The FTC has long opposed reverse payment settlements, also known as "exclusion payment" or "pay for delay" deals, where a generic company receives something of value from the innovator in exchange for agreeing to delay generic launch. The day before the authorised generics study was released, FTC chairman Jon Leibowitz said banning reverse payment settlements between innovators and generics firms would save US consumers about $3.5 billion annually (scripnews.com, June 24th, 2009).

Between fiscal years 2004 and 2008, about one quarter (38 of 152) of the final patent settlements submitted to the FTC contained provisions relating to authorised generics. 76 final settlements involved first-filer generics, and 20 of these featured agreements from the innovator not to launch an authorised generic during the exclusivity period and from the first-filer to delay generic market entry by, on average, 34.7 months past the settlement date.

Promises related to authorised generic launches are increasingly being used, instead of monetary payments, as a means to compensate the generic firm, the FTC said. An innovator may agree to refrain from launching a competing authorised generic to maximise the net present value of both the branded and generic products. The FTC cites documents from one innovator showing how a decision not to launch an authorised generic increased revenues of both the brand and generic companies.

Furthermore, innovators can use authorised generics agreements reached with subsequent ANDA filers as leverage in their settlement negotiations with first-filers, the FTC said. The report concludes that reverse payment agreements with authorised generics provisions can harm consumers by delaying first-filer generic entry and eliminating the benefit of price discounts from authorised generic competition during the first 180 days. "The consumer harm arises from the absence of authorised generic competition against an ANDA generic, not from the presence of authorised generic competition against an ANDA generic."

In a statement, the generics trade association GPhA reiterated its long-held position that authorised generics undercut the 180-day exclusivity period, calling this a "bad move" for consumers. "While we have not had an opportunity to read the entire FTC report, the fact is that authorised generics harm, not help, consumers. Authorised generics are yet another tactic that brand pharmaceutical companies have in their arsenal to keep affordable generic medicines from consumers," the group said.

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Health ministers unchanged in French cabinet shuffle

Roselyne Bachelot-Narquin remains minister of health after the French prime minister François Fillon reshuffled his cabinet. Mme Bachelot has been piloting a major healthcare bill through the French parliament. Proposed changes to the way hospitals are administered are the most controversial aspects of the bill, but it also contains provisions relating to the role of the pharmaceutical industry in patient assistance programmes. The minister issued a statement in May denying press reports that she had threatened to quit the government after President Nicolas Sarkozy appeared to have agreed to significant changes in the hospital legislation she had proposed. Valérie Pécresse has also kept her job as minister of higher education and research.

Caraco drugs seized by US Marshals

US Marshals, at the request of the US FDA, have seized all generic medicines and raw ingredients on the premises of Caraco at three Michigan plants, citing the firm's inability to take appropriate steps to correct violations of cGMP.

The action, which affects 33 generics in multiple strengths, was followed by a 43% decline in Caraco's share price. Caraco, the US subsidiary of India's Sun Pharmaceutical Industries, has had several recalls this year – the most recent for digoxin tablets due to size variability. According to Deborah Autor, director of the office of compliance with FDA's Center for Drug Evaluation and Research, the move is a preventive action.

"Seizures often result in court orders requiring companies to take steps to correct cGMP violations in their manufacturing processes," she added. These steps may include a temporary halt in the manufacturing process, hiring outside experts, writing new procedures, and conducting extensive training of employees. Caraco could fight the action while the seized goods are held. More often than not, however, the agency finds that firms are willing to agree to extensive correction actions, Ms Autor said.

In October 2008, the FDA sent Caraco a warning letter, citing significant deviations from cGMP relating to certain finished pharmaceuticals at its plant in Detroit.

This led to numerous recalls, but agency inspectors continued to find certain violations unresolved. The most recent inspection was completed last month, Ms Autor said, and revealed "serious deficiencies" in the controls of the company's manufacturing practices.

Some of the deficiencies were described as involving poor controls in tablet manufacturing, or higher than normal variability which repeatedly had not been addressed. Additionally, agency officials said that poor decisions were being made by management overseeing the Michigan operations. For one product – choline magnesium trisalicylate, an oral pain medicine – the action will create a shortage because Caraco has been the sole supplier, the FDA said.

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Supply chain rules not as bad as feared, say German companies

The 15th amendment to Germany's pharmaceutical law, AMG 15, voted through by the Bundestag in a late night sitting on June 18th, was not as bad as the local industry had feared regarding regulation of the supply chain.

The federal pharmaceutical industry association (BPI) had been concerned that the amendment would have prevented manufacturers from supplying pharmacists directly, and had they done so, would have faced financial penalties.

Much to the relief of the BPI, that was not among the changes voted through.

But it was decided that manufacturers must supply products to pharmaceutical wholesalers, the rationale being that distribution to some parts of the country would be uneven if wholesalers were not involved in the supply chain.

Speaking to *Scrip* at its offices in Berlin, the BPI said: "We have to deliver to wholesalers; they are big and important partners for us. But what we don't like is the government telling us that we cannot choose our partners."

The BPI says it is important that its members can deliver directly. The spokesman added: "We have never had problems with provision before."

Scrip understands that some wholesalers were concerned about their continued presence on the market if manufacturers opted for the direct-to-pharmacy distribution route.

Also unchanged is the wholesaler supply margin, which remains at 6%. Wholesalers had been lobbying for this to be a variable rate plus a fixed amount per pack. This change would be appropriate it felt, given the larger volume of lower-priced generic products circulating now.

But the proposal to change the drug prices order, the AMPreisV, was not agreed. The latest proposal was to give wholesalers 1.5% plus €0.70 per pack. "There will be no further progress on this issue in the current legislative period," said Wolf Bonner, member of the lower house health committee, in a recent Börsen-Zeitung report.

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More competition looms for Plavix

Sanofi-Aventis is facing yet more competition for its blockbuster antithrombotic Plavix (clopidogrel) after the EMEA gave the green light to several more generic versions. At the end of May, the EMEA's scientific committee, the CHMP, had recommended approval of Plavix generics from Teva, Acino and Pharmathen.

At its June 22nd-25th meeting, the committee OKd more generic versions from a range of companies including Acino (again), Mylan, Krka, Tad Pharma (part of Krka), Qualimed, HCS bvba and Norpharm Regulatory Services.

Plavix, Sanofi-Aventis's second-best selling drug, is patent protected in most European countries until 2013. However, while the active substance in Plavix is clopidogrel bisulfate, most of these generic versions contain different salts of clopidogrel – besilate or hydrochloride – which may not infringe the patent.

Indeed, Acino has been marketing a besilate salt of clopidogrel in Germany since July last year, having successfully fought off attempts by Sanofi-Aventis (and its co-marketer Bristol-Myers Squibb) to have the marketing authorisation suspended.

Nonetheless, once these new generics are approved by the European Commission, there may be some patent infringement action in the offing. Krka in particular may find itself in the firing line because (like Teva last month) two of its generics contain clopidogrel bisulfate.

Two other generic medicines were given positive opinions at the June meeting: a version of Pfizer's Viagra (sildenafil) from Krka and another generic version of GlaxoSmithKline's anticancer, Hycamtin (topotecan); a generic of Hycamtin from Actavis was OKd in May.

Following a referral procedure sparked by disagreements among the EU member state authorities regarding its safety, Helm Pharmaceuticals' Fentrix (fentanyl) was recommended for approval for severe chronic pain.

The committee also gave the go-ahead to Bayer Vital's Avalox/Octegra (moxifloxacin HCl) for community acquired pneumonia and complicated skin infections, for which serious public health concerns had been raised. The committee said the medicines should be approved but only for second-line use.

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NICE seeks comments on cost-sharing schemes

The National Institute for health and Clinical Excellence (NICE) is proposing changes to the way it takes flexible pricing schemes and patient access programmes into account as it evaluates health technologies for the national health service in England and Wales. A consultation document now being circulated reveals a willingness to consider new pricing arrangements both during and after a NICE appraisal, perhaps allowing sponsors a chance to reprice drugs that the institute initially finds inadequately cost-effective.

NICE's proposals follow the renegotiation of the UK's pharmaceutical price regulation scheme (PPRS) last year. The new agreement between the department of health and the ABPI allows manufacturers to submit proposals for patient access schemes or flexible pricing as part of ongoing or published NICE technology appraisals.

NICE points out that it has no responsibility for negotiating directly with manufacturers; it can only consider schemes and arrangements that have been approved by the department of health.

The institute proposes a rapid review of its guidance if a pricing or access scheme is approved within 12 weeks of the publication of a technology appraisal, and suggests that its appraisal committee will take no longer than six months to consider whether or not its guidance should be altered as a result.

The committee's decision is subject to appeal, but NICE is proposing that any appeal under this rapid review procedure should not concern points previously raised or points that could have been raised at earlier appeals.

Proposals for patient access or flexible prices agreed by the department more than 12 weeks after publication of NICE guidance will be considered in the standard review process; all published NICE appraisals indicate a tentative date for reconsideration of the evidence, usually one to five years later.

If an access or pricing scheme is approved before NICE's guidance is fully formed, the institute proposes fitting it into the appraisal process at an appropriate moment. It might be part of the initial application or it might follow the appraisal consultation document (ACD) that presents the institute's first draft of proposed guidance on the use of one or more technologies.

In the latter case, the institute might choose to issue a second ACD with changes, or it might choose to confirm its initial views and proceed to a final appraisal determination (FAD), which the institute seldom changes substantively before publishing binding guidance for the NHS.

The institute was already preparing updates to its guides on single- and multiple-technology assessments, and circulated a different set of proposals in December. NICE is still considering responses to that consultation and describes the new document on pricing and access schemes as an "extra addition". Comments on the latest proposals should reach the institute by July 20th.

Manufacturers have negotiated a number of novel pricing and access schemes with the department of health in the past two years, and positive recommendations from NICE have often followed:

- Janssen-Cilag's (Johnson & Johnson) Velcade (bortezomib) was recommended for treating multiple myeloma in the NHS on the condition that the company would refund the cost of treating non-responders;
- Novartis agreed to pay the drug cost of Lucentis (ranibizumab) for treating patients with wet age-related macular degeneration who required more than 14 injections per eye;
- Roche's Tarceva (erlotinib) was recommended for treating non-small cell lung cancer on the condition that it would cost no more than Sanofi-Aventis's Taxotere (docetaxel) in the same indication;
- Janssen-Cilag's Stelara (ustekinumab) earned a tentative NICE recommendation last month for the treatment of psoriasis after the company agreed that it would cost no more to treat patients weighing more than 100kg than lighter ones – essentially an agreement to provide two vials for the price of one;
- Merck Serono's (Merck KGaA) Erbitux (cetuximab) has been recommended in draft NICE guidance as a first-line treatment for some patients with metastatic colorectal cancer, but the institute says that the manufacturer should rebate 16% of the cost when it is used in combination with 5-fluouracil, folinic acid and oxaliplatin chemotherapy; and
- Celgene's Revlimid (lenalidomide) has been recommended for previously treated multiple myeloma, but only after the company agreed to pay the drug cost for patients who require more than two years of treatment.

But an innovative approach to pricing and access does not guarantee that NICE will look favourably on any product. The institute rejected GlaxoSmithKline's offer to pay for the first 12 weeks of treatment for patients with previously treated advanced or metastatic breast cancer.

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NICE rejection of Erbitux in head and neck cancer is final

Using Merck Serono's (Merck KGaA) Erbitux (cetuximab), in combination with platinum-based chemotherapy, to treat patients in England and Wales with recurrent and/or metastatic squamous cell cancer of the head and neck would not be a cost-effective use of UK national health service resources, an assessment agency has found.

NICE has published binding guidance that reiterates the conclusions of an earlier draft.

The institute published guidance last year, all but ruling out cetuximab in a similar indication, locally advanced squamous cell cancer of the head and neck. It said cetuximab could be used in a subset of patients with Karnofsky performance status scores of 90% or more and for whom all forms of platinum-based chemotherapy were considered inappropriate, but there are few – if any – patients who meet these criteria.

Cetuximab was also rejected in colorectal cancer indications.

In metastatic head and neck cancer, the NICE appraisal committee estimated that the cost of an additional quality-adjusted life year resulting from treatment with cetuximab plus platinum-based chemotherapy compared with platinum-based chemotherapy alone would be £121,367, and predicted an overall gain in survival of just over two months.

"This would mean the NHS making significant funds available for a very expensive treatment which may or may not benefit individual patients. Those funds would not then be available for treating other conditions with greater and more certain benefits for other patients," NICE said.

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Hong Kong reforms moving ahead despite swine flu delay

The H1N1 swine flu outbreak will not derail plans for the reform of Hong Kong's healthcare system, but will mean a delay to a second public consultation, the territory's secretary for food and health has said.

As part of the reform discussions, detailed proposals on supplementary financing options were due to be put out last year. But these were still being formulated and the current target was to release them for consultation by the end of the year, Dr York Chow said in reply to questions in the Legislative Council (LegCo).

Dr Chow conceded that bureau staff involved in preparing for the consultation had been assisting in the action against swine flu, which has infected around 785 people so far in Hong Kong.

Nevertheless, "Our work on healthcare reform will not stop," Dr Chow vowed, pointing to the overall importance of the reforms in controlling rising medical costs and coping with an ageing population.

He added that the epidemic would not affect the bureau's overall budget for the reforms, noting that recurrent health spending in 2009-10 would increase by around 5% to HK$35.7 billion ($4.6 billion), some 16% of total recurrent government spending.

The reform process and a first consultation were launched last year, with an emphasis on alternative financing mechanisms and the improvement of primary care. The bureau said at the time that the reforms should enable increased subsidies for "proven advanced drugs" as well as the reimbursement coverage of previously excluded products.

With such changes now further down the road, the HKAPI, the local association representing the research-based pharma industry, told *Scrip*: "We would like to see improvements to the existing system as soon as possible."

In line with its position paper on the reforms last year (scripnews.com, July 30th, 2008), one of the group's main concerns continues to be the link between patient payments and choice. "We want a system which provides sustainable financing and high quality care, along with a clear plan on how additional funding would be used effectively, not only generated," commented executive director Sabrina Chan. Given the current financial constraints on many people, any increase in contributions would have an impact on disposable income, and patients needed to know what additional benefits there would be, she said.

The association has also called for a general increase in healthcare funding and recognition of the broader value of innovative medicines.

Dr Chow told LegCo that public support had emerged from the first consultation for various ideas, including expanded public/private partnerships and expansion of the "safety net" to ensure the provision of care to those who needed it.

Some service reforms were already being worked as a result, including in the primary care and electronic health record areas, he noted. A working group on the first topic is due to make initial recommendations in the next few months, with pilot projects to strengthen chronic disease management due by the end of the year. In the health record field, a dedicated group will be set up in the third quarter, if funding is approved.

The health secretary also disclosed that, as part of preventive care initiatives, his bureau was planning to seek funding of around HK$1 billion from LegCo's finance committee for several vaccination programmes. The money would be used to provide free vaccinations against swine flu to four high-risk groups, and free pneumococcal and seasonal flu vaccines for people aged 65 years and over, he said.

Hong Kong began subsidising private-sector seasonal flu vaccinations for children last November.

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DNDi in deals with Merck & Co and university

The Drugs for Neglected Diseases initiative (DNDi) has signed two separate deals to identify new medicines to treat neglected tropical diseases. The first, involving Merck & Co, covers a range of neglected tropical diseases, including visceral leishmaniasis and Chagas disease. In the second agreement, the DNDi will provide £1.8 million over five years (for three years initially) to the drug discovery unit at the University of Dundee to identify molecules that will target the *Leishmania* parasite.

Thai trademark law changes would apply to drugs

Thailand is in the early stages of discussing changes to its intellectual property laws which may introduce new penalties for people buying or assisting the production and sale of counterfeit pharmaceuticals.

The potential amendments to the Trademark Act of 1991 and Copyright Act of 1994 are still under discussion and "things could change at any time," a lawyer with an international practice in Bangkok told *Scrip*.

The country is discussing the revisions mainly with the objective of cracking down on a recent proliferation of copyright and trademark infringements in the recorded media (CDs and DVDs) and branded goods areas.

Although any associated changes to the copyright law would not have much impact on the pharmaceutical sector, those to the trademark legislation would apply to all counterfeit items, including drugs, *Scrip* understands.

widening system

The main change to both laws would be to widen the current system of fines and other punishments to include any buyer of counterfeit products, as well as owners of property used in the storage, production or sale of such fake goods.

Drafts of the amendments have just been released for comment by the ministry of commerce's department of intellectual property, and remain subject to political and parliamentary approval. The ministry was not available for comment.

Thailand's current government appears to be taking a stronger line on IP protection, possibly to appease major trading partners such as the US.

watch list

Thailand remains on the US Trade Representative's priority watch list due to various IP concerns, including the controversial issuance of compulsory licences for a number of drugs several years ago.

But there has been a general strengthening of relevant legislation in the country over the past few years, including changes in 2000 which brought the local trademark law into compliance with World Trade Organization TRIPS norms.

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Looming price cuts worry Philippine R&D sector

The research-based industry in the Philippines has come out strongly against a government proposal which would halve the prices of top branded drugs in the country.

The local association representing the sector, the PHAP, said the move was "not necessary" given existing market competition and the wide availability of same therapeutic class alternatives.

Earlier this month, the Philippine department of health (DoH) submitted to President Gloria Macapagal-Arroyo a list of 22 most-prescribed branded products it said should be subject to the new maximum retail price (MRP) system. This included various cardiovascular, anticancer, antidiabetic and other drugs, with Pfizer's Norvasc (amlodipine) and Zithromax (azithromycin) among those targeted.

The MRP system itself forms part of the Universally Accessible Quality and Cheaper Medicines Act, passed by the country last year after lengthy political debate. This gave the president the authority to control drug prices via the MRP scheme in certain circumstances, such as pressing public health need, illegal price manipulation and unreasonable prices increases.

The PHAP is now arguing that the system should be viewed solely as an emergency measure, and that the cuts are unnecessary given the current competitive environment. This is evident from the strong growth of the local industry, which has been "driven by the entry of more generics following the patent expiry of several products in the last two to three years". This has led to greater generic use, with such competition only set to increase further from other patent expiries over the next few years, it said in a statement provided to *Scrip*.

The MRP system has also caught the eye of the US innovator association PhRMA, which said earlier this year as part of the US Special 301 trade process that it would like to see industry input into any MRP proposals.

Stressing the need to protect patents to encourage innovation, the PHAP says that it has already approached the DoH to discuss how its more than 50 members can improve access to medicines, particularly by poor and disadvantaged patients. Some firms, notably GlaxoSmithKline, have recently cut prices of some products in the Philippines.

The PHAP said it would continue to work towards "true healthcare reform", a core goal of which it sees as a system of universal healthcare coverage.

Despite the industry opposition, Senator Mar Roxas, a chief architect of the cheaper medicines law, called on the president not to heed industry lobbying and to immediately sign the MRP order. Price reductions so far under the new law had not been enough, and the local industry could grow further if the legislation were fully implemented, he said.

The law also modified the Philippines' intellectual property code to allow the early working of patents to ease generic entry, with the aim of supporting the domestic generics-led industry.

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Venezuela to revise intellectual property law

Venezuela is going to review its intellectual property system, says the government. Pharmaceutical patents are likely to be affected, although definite proposals are yet to be released.

In his weekly address to the nation, *Aló Presidente*, President Hugo Chávez asked ministers to look at the country's patent system. Shortly after, the minister for trade, Eduardo Samán, announced that his office would create a proposal for a new IP law to present to the national assembly.

It is not yet clear what exactly this will involve. "Patents have become barriers to production and we cannot allow them to continue as barriers to access to medicines, life or agriculture. For this reason we are reviewing all our patent legislation," said Mr Samán in a statement. However, in the same breath he said that legislation must be compatible with Venezuela's international treaties (which include the World Trade Organization TRIPS agreement).

Meanwhile, Arlen Piñate, director general of SAPI, Venezuela's IP office, said that the government would review the patent system to "convert it into a mechanism for contributing to national development and limiting dependency on foreign parties". Neither SAPI nor the ministry of commerce was available for comment. But it seems that there will be some debate on the matter with the pharma industry. Mr Samán has held talks with the CIFAR, the association representing the local and regional pharmaceutical industry, and CANAMEGA, the generic medicines industry. Both associations say that IP reform is necessary, according to local press reports.

It is unclear whether CAVEME, which represents the R&D-based industry, was involved in the talks. Neither CIFAR nor CANAMEGA was available for comment, while CAVEME was unable to comment in time for this article.

There has already been concern about Venezuela's approach to IP. The country remains on the US Trade Representative's priority watch list, on the recommendation of PhRMA, the US pharma industry association. In its 301 submission for 2009, it claims that Venezuela is in violation of a number of TRIPS articles. SAPI has not granted any pharmaceutical patents since 2002, the same year that Venezuela stopped protecting clinical trial data, it says.

Amid concerns about access to medicines, the government has been pushing for "pharmaceutical sovereignty" to reduce dependence on private and multinational firms for healthcare provision.

In May, Mr Chávez opened SEFAR, a state-owned manufacturing plant for producing around 100 products, including anticonvulsives, antihypertensives, antibiotics and TB treatments. The health ministry declared the plant to be "another step towards scientific and technological independence in medicines" and announced that another state-owned pharmaceutical plant would soon be under construction.

But improving access to medicines could be better achieved through developing comprehensive IP rights, argues Lawrence Kogan, president of the Institute for Trade Standards and Sustainable Development. "Venezuela needs to develop a national IP system that can promote its economic and technological development and reduce the likelihood that it will become a 'welfare dependent state'," he told *Scrip*.

Strong IP rights attract foreign investment, a significant amount of which comes from multinationals, said Mr Logan. They also stimulate high-quality technology transfer through licensing, joint-ventures or establishing wholly owned subsidiaries, boosting the potential for developing domestic innovation, he said.

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POLICY & REGULATION ROUND-UP

Vermont's governor James Douglas signed into law in early June what is believed to be the strictest gift and **payment disclosure law** in the US for doctors and other medical professionals – and far more sweeping than comparable gift disclosure laws in other states. The new law, which strengthens an existing disclosure law in the state, bans nearly all industry gifts, with few exceptions; these include free meals, to doctors, nurses, medical staff, pharmacists, health plan administrators and healthcare facilities.

A former **Pfizer** regional sales manager, Mary Holloway, has been sentenced for off-label marketing of the COX-2 inhibitor, **Bextra** (valdecoxib), a violation of the FD&C Act, according to the US Attorney's Office for the District of Massachusetts. Sales of the product were suspended globally in April 2005 by Pfizer, which had gained it through its acquisition of Pharmacia.

Pfizer has prevailed over **Teva Novopharm** in its Canadian patent infringement litigation involving a generic version of **Viagra** (sildenafil). A federal judge has declared that the company has "met its legal burden" in establishing the validity of patent No 2,163,446.

UCB and **Sepracor** have filed suit in the US District Court for the Eastern District of North Carolina against **Synthon Pharmaceuticals**, alleging patent infringement related to its generic version of **Xyzal** solution 2.5mg/5ml, thus triggering a 30-month stay of approval. Sepracor had received notice that Synthon and its partner Perrigo had filed an ANDA with a paragraph IV challenge relating to the only Orange Book-listed patent (the '558 patent); Synthon and Perrigo seek to market a generic before 2012.

Teva Pharmaceutical Industries has sued the US **FDA** because of its loss of first-filer marketing exclusivity on generic versions of **Merck & Co**'s antihypertensives, **Cozaar** (losartan potassium) and **Hyzaar** (losartan plus hydrochlorothiazide). The case involves situations where a brand firm has voluntarily delisted patents. Teva believes the agency's interpretation of the intersection between the delisting mechanism and the 2003 Medicare Modernization Act (MMA) is unsustainable.

The US **FDA** has informed Takeda's **Millennium Pharmaceuticals** unit that its inclusion of a double-entendre around a cancer term "CR" in a mailer for **Velcade** (bortezomib) relating to the ASCO 2008 annual meeting in Chicago went beyond what is permitted in a reminder piece, and is thus violative of drug marketing law. The mailer was provided to attendees of the conference in registration materials.

The recent launch of a **study** on the value of incremental pharmaceutical innovation by the **US-India Business Council** and the **Coalition for Healthy India** in Washington was no ordinary launch, or so it seems given the multitude of reactions the event triggered among stakeholders. The study targets the much debated and controversial Section 3(d) of India's Patents Act that deals with inventions that are not patentable in India.

China is bolstering its social security reserves through a requirement for all state-owned enterprises (SOEs) trading on domestic stock exchanges to donate to the **National Social Security Fund** 10% of the stock offered at the time of listing. The State Council order will apply to all SOEs which have floated in China since late 2005 or will do so in the future. The aim is to inject new funds into the strategic reserve fund, which supports public pension and elderly care insurance programmes.

China's **Sinovac Biotech** expects to produce the first batch of a new vaccine against the influenza A (**H1N1**) virus by the end of July. The firm has received its first order for the vaccine from the Chinese government, for four million doses for delivery by the end of September. The batch will be used initially to inoculate two million people at high risk of exposure to the new flu strain. Sinovac expects to supply a total of around 10 million doses to the government.

The value of **French pharmaceutical exports** grew by more than 10% last year, reaching €21.2 billion. Pharmaceuticals represented 5.9% of all exports from France, putting the sector in third place behind the aerospace (7.7%) and automotive (7.6%) industries. France also spent more on pharmaceutical imports last year: around €14 billion, up by 5.2%. Net exports of €7.1 billion were 22% higher than a year earlier.

The **Spanish ministry for science and innovation** and the autonomous community of **Madrid** have signed an oncology **R&D collaboration** protocol that should be a boon for translational research. The national oncological clinical research centre will run the research project from the Fuenlabrada university hospital in Madrid. It will have access to all the hospital facilities that it needs, and a large patient pool.

13 new transnational **research consortia** focused on identifying therapeutic targets in a range of pathogenic micro-organisms are up and running in the **EU**, and through a second funding round are to receive €16 million over the next three years. The consortia are part of the ERA-NET PathoGenoMics network set up in 2004 through the EU's sixth framework programme.

A combination therapy for **sleeping sickness** provides better effectiveness and easier administration than current monotherapy treatments, a study published in *The Lancet* has found. Nifurtimox-Eflornithine Combination Therapy (NECT) is also more cost-effective and may be less susceptible to drug resistance than current treatment eflornithine, revealed the Phase III study, which compared the therapies in second-stage human African trypanosomiasis.

The **Australian Prescriber**, which undertakes independent reviews of drugs, says there has been an improvement in the willingness of pharmaceutical firms in **disclosing information** that supports the Australian approval of their products. The editorial executive committee of the magazine says there has been an improvement since previous reports on transparency were published in 2005 and 2007.

The **New Zealand** health minister, Tony Ryall, has given the go-ahead for local biotech firm Living Cell Technologies to conduct a Phase I/IIa clinical trial of its **Diabecell implant**, which involves the transplantation of pig islet cells into insulin dependent diabetics. The trial, which aims to normalise blood glucose levels in type 1 diabetes and therefore eliminate the need for daily insulin injections, should start within the next two months.

This is a round up of Scrip's policy & regulation news. Read the full stories plus others at scripnews.com

Generex Biotechnology, a US company focused on drug delivery for metabolic diseases through the inner lining of the mouth, has appointed ***Stephen Fellows*** vice-president of finance. He was previously chief financial officer of Sona Mobile Holdings.

Scott Byrd has joined Cadence Pharmaceuticals (US) as senior vice-president and chief commercial officer. He joins from Lilly, where he was most recently US brand leader for prasugrel. Before that, he was senior director of global brands, cardiovascular and acute care.

MacroGenics, a private US biotechnology company development and delivery of novel biologics for autoimmune disorders, cancer and infectious diseases, has elected ***Paulo Costa*** to its board as an independent director. Mr Costa, who has more than 35 years' experience in operations and commercialisation in the pharmaceutical industry, is the former president and CEO of Novartis US.

Synta Pharmaceuticals (US) has named ***Dr Vojo Vukovic*** senior vice-president and chief medical officer. He was previously vice-president of clinical research, a position he has held since January. ***Dr Eric Jacobson***, who recently announced his resignation as senior vice-president and CMO, will be leaving the company after a transition period. Dr Vukovic was previously global medical lead for Sutent (sunitinib) and axitinib in several cancer indications at Pfizer.

The US Senate has named ***Dr Eric Goosby*** the next US Global AIDS Co-ordinator. Dr Goosby brings over 25 years' experience to the role, including serving as CEO and chief medical officer of the Pangaea Global AIDS Foundation and deputy director of the White House National AIDS Policy Office under the Clinton administration, and has been a practising physician treating HIV patients since the 1980s. As co-ordinator, Dr Goosby will consider future ways to continue fighting the pandemic, while working with the Obama administration.

Halozyme Therapeutics (US) has named ***Dr Michael Shepard*** vice-president of discovery research. He has more than 25 years' experience in the biotechnology industry, having most recently been founder and president of Receptor BioLogix. At Genentech, Dr Shepard led the team that discovered the breast cancer drug Herceptin (trastuzumab). In 2007, he shared the Warren Alpert Prize from Harvard Medical School in recognition of the achievement.

Transition Therapeutics, a biopharmaceutical company developing novel therapeutics for diseases with large markets, has appointed ***Laura Agensky*** vice-president of clinical operations. Ms Agensky has been with Transition for eight years managing the implementation of clinical trials; prior to this she held a number of clinical development roles at pharmaceutical, biotech and consulting organisations.

WuXi PharmaTech, a pharmaceutical, biotechnology and medical device R&D outsourcing company with operations in China and the US, has named ***Felix Hsu*** senior vice-president of WuXi AppTec US. Mr Hsu joins the company after a 14-year career at Medtronic, where he had served as director of heart valve worldwide marketing; vice-president of business excellence; and vice president of cardiac surgery for Asia-Pacific, based in Hong Kong; and vice-president of supply chain integration, based in Minneapolis.

INC Research, a US contract research organisation, has named ***Dr Tom Zoda*** senior vice-president of neuropsychiatry to its central nervous system (CNS) team. He will provide an oversight of all psychiatry and neurology projects and drive overall growth of the CNS division. Dr Zoda previously worked for PPD for more than 10 years, most recently as executive director for global strategic development, CNS. Before that, he worked for Tanox Biosystems.

The US speciality pharmaceutical company Hemispherx Biopharma has appointed ***Robert Dickey*** senior vice-president. The newly created role will bring together activities relating to fund raising, strategic partnering and finance functions. Mr. Dickey has more than 12 years' experience in biotech senior management, following an 18-year career as an investment banker.

In search of a gold standard in multiple sclerosis

Advanced dosage and delivery technologies promise improved quality of life for multiple sclerosis patients, while some companies are betting on being the first to develop the breakthrough blockbuster therapy. A step change in MS treatment is on the cards, explains Dr Andrea Taylor

Multiple sclerosis (MS) affects about 2.5 million people worldwide and the condition has spawned a $7 billion market that is estimated to double by 2013, making it a lucrative target for pharmaceutical companies seeking to develop new blockbuster products. Unlike many disease areas in which a clear market leader exists, there has historically been no clearly differentiated gold standard first-line therapy for relapsing remitting MS (RRMS; see Figure 1).

There is also a clear need for improvements in treatment efficacy, in other words a real financial opportunity for new innovations. A number of promising developments in the clinical pipeline suggest the MS treatment landscape to be dynamic and potentially on the brink of major change.

Historically, there have been four major disease-modifying drugs that reduced the rate of progression of RRMS (a fifth, Tysabri (natalizumab), was re-introduced in 2006, as discussed below).

Three of the formulations are interferons; two of interferon beta-1a (Avonex and Rebif) and one of interferon beta-1b (Betaferon/Betaseron; see Table 1). The fourth disease-modifying drug is Copaxone, a formulation of glatiramer acetate.

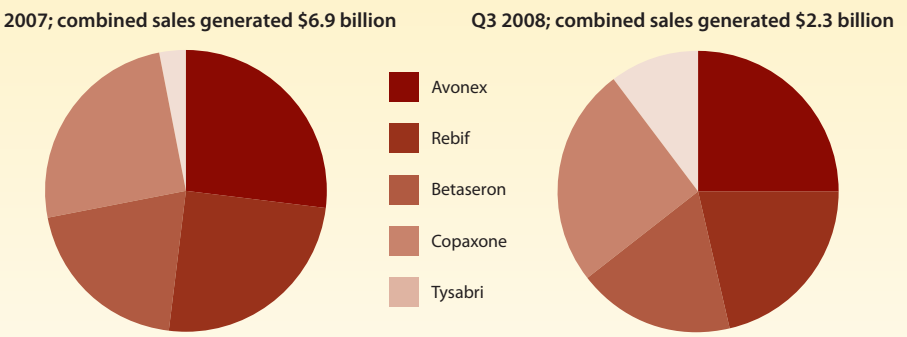
While these drugs are reasonably well tolerated by patients, have long safety records and help to manage the symptoms of MS fairly well, key opinion leaders (KOLs) only consider them to be "about one-third of the way to a cure", according to a study conducted by the authors.

None of the four treatments has achieved a dominant market position. They all occupy an almost equal market share, with prescribing practices often dependent on regional and clinician preference-based differences.

Recent head-to-head trials such as the Merck Serono-sponsored REGARD study (Rebif vs Glatiramer Acetate in RRMS) have shown little difference in clinical efficacy between drugs. The 764-patient REGARD trial reported in 2007, demonstrating no clinical-efficacy difference between Rebif and glatiramer acetate.

Similarly the 2,244 patient BEYOND trial (Betaferon/Betaseron Efficacy Yielding Outcome of a New Dose), sponsored by Bayer Healthcare, reported in 2008 and demonstrated no significant difference in efficacy between Bayer's Betaferon/Betaseron and Copaxone. In both trials the safety of all the drugs was demonstrated.

Figure 1: Global market share of the top five selling multiple sclerosis drugs



Source: Cambridge Consultants analysis

Copaxone is holding market share slightly better than the interferons, perhaps reflecting its perceived ease of use compared with interferons, which can cause side-effects including flu-like symptoms, liver abnormalities and depression.

new standards in efficacy

The "new drug on the block" is Biogen Idec/Elan's novel once-monthly Tysabri. It has been considered the new standard with regards to efficacy since it was relaunched in 2006. Tysabri is a humanised monoclonal antibody that is believed to reduce the ability of inflammatory immune cells to attach to and pass through the cell layers lining the intestine and the blood-brain barrier.

In the most recent clinical data, released in February, Tysabri appears to result in five times as many patients remaining free from disease activity over a two-year period compared with placebo. It is significant that the response to MS therapy is described in terms of freedom from disease activity, as opposed to simply a reduction in relapse rate, the common endpoint by which disease-modifying drugs have traditionally been measured.

The data seem to reflect the experience of KOLs interviewed by the authors over the past year. The KOLs report that Tysabri is much more efficacious than traditional treatments and is "about half way towards a cure".

Despite the potential step-change in terms of efficacy, Tysabri is unlikely to be widely used. It is currently a second-line treatment for patients who do not respond well to the four major disease-modifying therapies. The reason? Serious safety concerns. Just one year following Tysabri's original approval by the US FDA in 2004, it was withdrawn after being linked to three cases of the rare neurological condition, progressive multifocal leukoencephalopathy (PML). PML is an incurable disease with diverse symptoms dependent on the extent and location of damage to the brain.

Since the relaunch of Tysabri in the US and its first international approval in 2006, both under a special prescription programme, there have been a further 10 cases of PML, including three diagnosed in June, and one death in an MS patient who had received 14 infusions of the drug.

While the prescribing information cites PML as a possible side-effect for one in every 1,000 patients, clinicians face a

Table 1: Disease-modifying multiple sclerosis therapies

Product class	Name	Manufacturer
interferon beta-1a	Avonex	Biogen Idec
interferon beta-1a	Rebif	Merck Serono
interferon beta-1b	Betaferon/Betaseron	Bayer Schering Pharma
interferon beta-1b	Extavia[1]	Novartis
glatiramer acetate	Copaxone	Teva Pharmaceuticals
natalizumab	Tysabri	Biogen Idec/Elan

[1]Novartis gained rights to its own branded version of Betaseron/Betaferon in agreements with Bayer Schering Pharma related to the acquisition of Chiron. Extavia was launched in the EU in January 2009.

dilemma in weighing up the benefits of a more efficacious drug with the potential that the patient may end up with a second incurable disease.

Thus there may be a decrease in the number of potential "new starts" on the drug. And some of the 48,000-plus patients currently receiving Tysabri may choose to discontinue due to concerns over safety.

Shares in Biogen Idec sank this week following the announcement of the most recent case of Tysabri-related PML. In February the company indicated that it would struggle to meet its goal of 100,000 Tysabri patients by 2011. Yet another incident of PML puts that target even further out of reach. With Tysabri unlikely to become a market-dominating force, the landscape is left wide open for an efficacious therapy with an improved safety profile.

oral therapies: the race is on

One major drawback with all currently available therapies is that they have to be administered via regular intravenous or subcutaneous injections or, in the case of Tysabri, by a once-monthly infusion at hospital. There is a clear need for safer and more efficacious drugs offering a more patient-friendly method of administration.

At present there are five oral MS treatments in Phase III trials: Novartis's fingolimod, Merck Serono's cladribine, Biogen Idec's BG12, Sanofi-Aventis's teriflunomide and Active Biotech/Teva's laquinimod. These companies are eyeing a prize worth $1.3 billion a year if patients switch from injectable drugs.

The products from Teva, Sanofi-Aventis and Biogen Idec may not reach patients until 2012, but both Merck Serono's and Novartis's drugs are on schedule to be approved in 2009.

Merck Serono released promising Phase III data in January, indicating that cladribine reduced relapses by 60% compared with placebo. These data place cladribine on a par with fingolimod. In addition, post-hoc analysis of the same CLARITY trial (Cladribine Tablets Treating MS Orally) released in June demonstrated that short-course oral treatment resulted in rapid and sustained improvements in clinical and MRI imaging outcomes accompanied by rapid and sustained effects on blood cell subtypes implicated in the pathogenesis of MS.

Fingolimod is in three Phase III trials that are all set to report this year. Encouraging preliminary data from 1,292 patients taking either fingolimod or Avonex were released in December 2008. In this head-to-head trial the annualised relapse rate for fingolimod was 0.16 compared with 0.33 for the Avonex arm.

Will the new class of oral MS drugs have the disruptive effect on the market that is widely anticipated? The answer is unlikely to be known until later this year when final test results on fingolimod and cladribine demonstrate how safe and, ultimately, how adoptable each drug is.

> There is a clear need for safer and more efficacious drugs offering a more patient-friendly method of administration

In the data released for cladribine this year, four of the 1,326 patients developed cancer, albeit all in different sites. While not considered significant by independent moderators, this finding nevertheless raises a red flag over the long-term safety profile of the drug.

Similarly, in the fingolimod trials to date, there have been two reported cases of fatal infection and seven incidences of successfully-treated skin cancer. Concerns over cancer and opportunistic infection are real barriers to what could be substantial first-line use.

Dr Daniel Kantor, an assistant professor of neurology and the director of the Comprehensive Multiple Sclerosis Center at the University of Florida, says: "We should be careful not to think that all RRMS patients will switch to oral medicines since there is, and will be, serious safety concerns with these newer medicines. The older injectable medicines may be annoying, but no-one has ever gotten cancer or died from them. We may all be hopeful and optimistic, but we should also be realistic and patient."

Manufacturers of traditional injectable medicines are clearly mindful of the dosing issue and are exploring both delivery solutions (see below) and drug modifications in a bid to remain competitive as new therapies offer greater patient convenience. In June Biogen Idec announced that it had begun enrolling for its Phase III randomised double blind placebo controlled ADVANCE trial designed to evaluate the efficacy and safety of PEGylated interferon beta-1a in RRMS patients. The PEGylated version of Avonex offers the possibility of 2-4 week dosing as the PEGylation protects interferon beta-1a from degradation.

repurposing oncology drugs

Product repurposing offers an alternative and significantly cheaper strategy for tapping into the MS market. Bayer Schering Pharma and Genzyme are trialling the B-cell lymphoma drug Campath (alemtuzumab) for MS; it is currently in Phase II trials, with approval expected in 2011.

Phase II head-to-head trial data against Rebif were compelling and MS clinicians widely believe that Phase III results will show Campath to be highly efficacious in the treatment of MS. Moreover, Campath offers the potential of once-yearly infusions, ultimately trumping the attractiveness of a daily oral tablet.

Genzyme's confidence in Campath was underscored by its recent announcement that it would acquire the product from Bayer as part of a $2.8 billion deal (along with two other anti-cancer drugs, Fludara (fludarabine) and Leukine (sargramostim)). A leading MS expert commented: "There are no orals coming to the market that are less frequent than once-daily. Therefore, I think that a once-yearly infusion [with no need for patients] to think about [their] medication will be very attractive in comparison."

Campath is a humanised anti-CD52 monoclonal antibody that targets white blood cells (lymphocytes). Its immunosuppressant properties leave patients open to opportunistic infections. In addition, around one-third of patients treated with Campath develop thyroid problems and a further subset (6%) will develop immune

thrombocytopenic pupura (ITP), a condition in which the platelet count drops, leading to failed blood clotting. This ultimately carries a risk of internal bleeding.

While both the thyroid and ITP conditions are detectable and curable, these side-effects mean that Campath will need to be prescribed at specialised centres that offer the necessary support in terms of blood work and associated monitoring.

This requirement for monitoring, alongside the aggressive nature of the drug, will undoubtedly impact Campath's adoption in the MS market. Campath will likely be a second-line treatment to which patients move as their condition progresses. However, with fewer potentially fatal side-effects, it may well be considered in preference to Tysabri.

stem cells

This February saw headlines proclaiming that a cure had been found for MS. These followed the publication of data demonstrating the use of stem cells to reverse the effect of the condition.

While such claims may have been premature, the work conducted by an international team under the leadership of Dr Richard Burt of Northwestern University in the US provide a glimpse into the longer term potential of MS therapy.

The treatment involved harvesting stem cells from the bone marrow of MS patients and freezing them while conventional drugs were administered to remove the immune or lymph cells causing damage. The bone marrow cells were then replaced to replenish the immune system.

Remarkably, none of the 21 adults with RRMS who received a stem cell transplant showed any deterioration in symptoms over the three-year study period. This is not the first time the treatment, known as autologous non-myeloblative haemopoietic stem cell transplantation, had been tested. But it is the first time it has been successful. This is largely because in previous attempts the treatment has been trialled on patients with the more advanced secondary progressive form of the disease. By treating RRMS patients with less advanced disease states, Dr Burt claims that improvements in many parameters of MS can be improved. While superficially impressive, the data are highly preliminary. Major safety concerns from potential infections and tumours do not make this a viable treatment at present. It should also be noted that cyclophosphamide, a drug administered during the course of the study, is a strong chemotherapy agent already used in the treatment of MS. Nonetheless, the study highlights the dynamic nature of research in this field and the new approaches that are being pioneered.

new delivery devices

So have the conventional disease-modifying drugs had their day? Perhaps not yet. The manufacturers of "the big four" are unlikely to relinquish their billion-dollar revenues without a fight. Alongside new drug developments, new delivery devices are being developed to differentiate existing drugs on the market.

Given the limited safety records of the new drugs progressing through the pipeline, it is unlikely their launch will result in the immediate conversion of all MS patients from older therapies.

By contrast, Merck Serono and Bayer Schering Pharma have already recognised that improving the delivery of Rebif and Betaseron/Betaferon could improve patient compliance, potentially leading to the transfer of patients onto drugs packaged in new delivery offerings.

In 2008 Bayer Schering Pharma launched the Betaject Lite autoinjector, a device with a 30-gauge needle, the smallest needle of all disease-modifying therapies for use with Betaseron/Betaferon.

Merck Serono is looking to advance treatment delivery even further with its Rebismart electronic delivery device, which has just been launched in Canada and the EU. The device is used with multi-dose Rebif cartridges, each of which contains one week's worth of medication. Originally designed for parents to administer growth hormone to their children, the device has a hidden needle that offsets some of the anxiety associated with needle phobia. Skin contact calibrated delivery and electronic counting features monitor dosage and aim to improve patient compliance.

Sceptics complain of limited meaningful improvement and the fact that the newer devices do little to prevent needle fatigue setting in. That said, anything that can improve compliance and thus the effectiveness of well established treatments with proven safety records, will likely be quickly adopted even if they do not radically alter the treatment landscape.

The face of MS treatment looks set to change and there is great opportunity for a market leader to establish itself and attain blockbuster status.

On a more sobering note, however, such positive developments sadly contrast with underwhelming R&D activity in the more debilitating progressive forms of the disease, which remain largely incurable at present. One can only hope that the changing face of the RRMS landscape will spill over into these advanced forms of the disease before long.

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