For the week of October 4, 2004

BioCentury

BioCentury 100™ Indicators

Week ended 10/1/04

PRICES	VOLUME
1485.31	448.5M shrs
up 2%	up 9%

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By Steve Edelson
Senior Writer

The public markets are expected to be volatile at least until the November elections in the U.S., and, accordingly, safe haven biotech stocks — companies with profits — are performing better than their loss-making counterparts. Indeed, the profitable constituents of the BioCentury 100 Index began to separate themselves from the non-profitable companies at the end of April.

If defensive investing is the prognosis for the remainder of the year, biotech will not be shut out, as an increasing number of companies have turned the profit corner, or at least have a growing revenue stream *(see "Performance by Profitability," A2)*.

In addition, there's a queue of late-stage milestones among loss-making companies coming up in the quarter that should keep investors interested in their paper. As a result, bankers polled by BioCentury think that such companies will not have problems tapping into the markets.

However, many buysiders, bankers and VCs expect a muted fourth quarter for new issues. Although there may be a trickle of new filings — two companies put their hats into the ring last week — the consensus is that the majority of companies already in the queue won't go out until 2005.

And on the follow-on front, PIPEs and other directed placements may be the vehicle of choice for low cap public companies with downtrodden prices to match.

'Money will go to companies with parameters that can hold up their valuation, such as revenues or earnings. These parameters allow investors to judge whether a stock is expensive or cheap.'

— Thomas Weisel's Jim Scopa

Election complexion

Right now, it is hard to tell whether the biotech bull that began on March 7, 2003, has been put out to pasture. Both biotech and the overall markets are up from last year's low point, but all of these groups gave back some gains in the third quarter. Biotech led the downward charge. Not helping the group was a relatively small and bland slate of approvals in the third quarter *(see "3Q Wrap-up," A10)*.

Michael Cohen, managing director at Deutsche Bank, said that bullish or bearish sentiments can vary from week to week. "Given the volatility with the election and other macro issues, a couple of up or down weeks can flip us into one or

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BIO-Europe update

A month remains until BIO-Europe 2004 convenes in Cologne.
Please see announcement following A26.

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the other."

The U.S. election is the key uncertainty weighing on the market. But in looking past Nov. 2, some buysiders think that the result will have little effect on public biotechs, regardless of who wins.

In the event that the Democrats take the White House, MPM's Kurt von Emster expects that not much will change in the near term. He noted that Mark McClellan, administrator of the Centers for Medicare & Medicaid Services, "has said that reimbursement is set for 2005. Thus, a new administration probably won't be able to change CMS's direction until 2006. In general, the investor standpoint is that a Republican victory would be better, and if Bush if reelected there probably will be a short relief rally."

Sven Borho of OrbiMed Advisors also thinks that the election outcome won't matter much. "It will have minor effects on biotech," he said. "At the end of the day, biotech has been smart about dissociating itself from the pharma group and the problems with the pharma sector. I don't think biotech will be harmed if Kerry is elected and I don't think there will be a relief rally if Bush wins."

However, Thomas Weisel banker Jim Scopa suggested that a Democratic victory could have a negative effect on the IPO window and advised companies to try to go out now.

"People are suggesting that potential IPOs be booted into the first quarter of 2005. I don't think this is a good idea, because there's the potential for a repeat of the Bill and Hillary show in 1993 — an administration that's OK with talking about reimports and price controls. I understand why people would want to have the uncertainty of an election out of the way, but the uncertainty in 1992 would have been better than the negative certainty of 1993."

Go big

Regardless of what happens after the election, the event itself is a source of uncertainty. And in volatile markets, investors predictably gravitate towards large cap names. The third quarter was no exception, as the Dow Jones and Amex Pharma indexes fell only 3% and 5%, respectively, while the NASDAQ dropped 7%. The pharma index took a hit in the last week of the quarter, when Merck & Co. Inc. (MRK, Whitehouse Station, N.J.) announced it was pulling its Vioxx rofecoxib COX-2 inhibitor from the worldwide market *(see "Deconstructing the COX-2 Difference," A13).* MRK fell $12.07 (27%) to $33 on Sept. 30, and the pharma index slipped 2.6%.

The BioCentury 100 Index was off 8% last quarter. But the biotech group remains 2% above water for the year, while each of the broader market indicators is flat or in the red. *(see "Index Performance," A10).*

Moreover, the performance of biotech stocks valued above $2 billion has proven to be the exception to the flight to quality rule. That group was off 8% last quarter, snapping a streak of seven consecutive quarters in which the top tier posted a quarterly gain *(see "Results by Market Cap," A10).*

Because of this group's strong performance for nearly two years, Deutsche Bank's Cohen suggested that these stocks may have been "priced for success. In light of the macro issues before us, people may think that the likelihood of downward movement is higher than upward. Thus they might take some skin out of the game" with stocks on which they made money.

Many bankers and investors look for the large cap slide to reverse course this quarter. SG Cowen banker Annette Grimaldi is a member of this camp. "In a volatile market, you go for liquidity, stability and profitability," she said. "This means pharma and big cap biotechs."

JMP banker Bob Kerry noted that the group "has been seriously discounted over the last four months despite solid fundamentals. There have been product approvals and late stage data, and no cataclysmic blowups that would cause the group to head south. All these factors should make people take notice" in the fourth quarter.

Daniel Omstead, president and CEO of Hambrecht & Quist Capital Management, suggested that big cap growth investors might start to look to big cap biotechs with depressed stock prices instead of their pharma counterparts. "I see big cap growth investors talking about Amgen, Genentech and Genzyme as companies in their universe," he said. "If they have success with those names, their attention potentially could turn to other, smaller profitable names."

And as earnings season gets underway, von Emster suggested a good way to play the fourth quarter is to bet on "earnings stories with momentum," such as Gilead Sciences Inc. (GILD, Foster City, Calif.) and Genzyme (GENZ, Cambridge, Mass.).

In the second quarter, GILD reported EPS of $0.49, which blew through the Street's $0.36 estimate and was up 7% from the same period in 2003. The company's revenues increased 33% quarter over quarter to $317.9 million from $238.9 million.

Similarly, GENZ's second quarter EPS of $0.44 beat the

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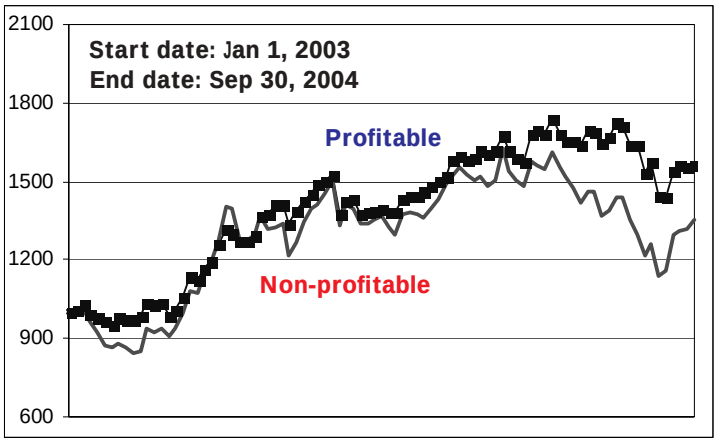
Performance by profitability

Profitable biotech companies have been outperforming non-profitable companies since the beginning of 2003, with most of the divergence coming since the beginning of April this year. Based on indexes constructed from companies in the BioCentury 100 index, profitable companies are up 58% since Jan. 1, 2003, compared to a 35% gain for their non-profitable siblings. Twenty-eight companies in the index were used to construct a price-weighted, profitable biotech index, while 69 companies were used to benchmark the non-profitable group. Three non-profitable companies were excluded because they were added to the index after Jan. 1, 2003.



4Q milestones

Selected fourth quarter milestones in Canada and the U.S.

Company	Product	Indication	Milestone
Connetics (CNCT)	Extina	Seborrheic dermatitis	11/26 PDUFA date
Connetics (CNCT)	Actiza	Acne	10/24 PDUFA date
CoTherix	Ventavis	Pulmonary arterial hypertension	12/31 PDUFA date
Epix (EPIX)	MS-325	Vascular imaging	Mid-October PDUFA date
Eyetech (EYET)	Macugen	Wet age-related macular degeneration	12/17 PDUFA date
La Jolla (LJPC)	Riquent	Lupus	Mid-October PDUFA date
SuperGen (SUPG)	Orathecin	Pancreatic cancer	11/26 PDUFA date
Cardiome (TSE:COM; COMRF)	RSD1235	Acute atrial arrhythmia	Ph III data
Corgentech (CGTK)	Edifoligide	Peripheral bypass vein graft failure	Ph III data
ConjuChem (TSE:CJC)	DAC:GLP-1	Type II diabetes	Ph II data
Amylin (AMLN)	Exenatide LAR	Type II diabetes	Ph II data
Amylin (AMLN)	AC137	Obesity	Ph II data

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consensus estimate of $0.40. The company also raised its sales guidance for three of its key drugs: Renagel sevelamer, a phosphate binder to treat end-stage renal disease (ESRD); Fabry's disease drug Fabrazyme agalsidase beta; and Cerezyme enzyme replacement therapy for Gaucher's disease.

Another positive message to take away from the sour third quarter is that the typical fourth quarter window dressing — selling strong performers to lock in gains — might not occur.

"This hasn't been a big enough year where you need to do window dressing," said von Emster. "If biotech were up 30% there would be some."

Borho also doesn't expect much window dressing, which he said should clear the way for biotech "to have a strong fourth quarter."

One tier down

Fortunately for the rest of the sector, investors probably won't be looking only to rekindle their interest in the top tier stories.

Thomas Weisel's Scopa said investors are already comfortable with the smaller companies that are turning a profit. "This has been a good place to invest and we have more of these companies in biotech and specialty pharma than we did five years ago," he said. "In the end, money will go to companies with parameters that can hold up their valuation, such as revenues or earnings. These parameters allow investors to judge whether a stock is expensive or cheap."

Cohen thinks that investors will find a sweet spot with companies valued in the upper millions to the low billions, where modest revenues can have a big impact on EPS. "With the bigger companies, it takes a lot to move the dial," he said.

Investors also believe that companies in the red won't be left out in the cold if they have a late stage story to tell.

A prime example is Sepracor Inc. (SEPR), which last month pulled in $500 million in a note deal *(see BioCentury, Sept. 20)*. The company isn't expected to turn the corner in the near term, but it does have a Dec. 15 PDUFA date for insomnia compound Estorra eszopiclone.

SEPR (Marlborough, Mass.) also has a revenue stream. For the first six months of 2004, the company posted revenues of $169.4 million, up slightly from $161 million in the same period in 2003. Its six-month operating loss was $114.7 million, which included a $30.7 million charge for a terminated deal.

In addition to Estorra, at least seven other compounds have PDUFA dates in the fourth quarter. Most important are Macugen pegaptanib from Eyetech Pharmaceuticals Inc. (EYET, New York, N.Y.) and Pfizer Inc. (PFE, New York, N.Y.) to treat wet age-related macular degeneration (AMD); MS-325, a vascular imaging agent from Epix Pharmaceuticals Inc. (EPIX, Cambridge, Mass.) and Schering AG (FSE:SCH; SHR, Berlin, Germany); and Fosrenol lanthanum carbonate from Shire Pharmaceuticals Group plc (LSE:SHP; SHPGY, Basingstoke, U.K.) *(see "4Q Milestones").*

Thus, von Emster told BioCentury that another key investing strategy in the fourth quarter will be to "play the potential new approvals."

With this basket of events on the near term horizon, many Street watchers expect that these companies will be relatively unaffected by macro issues. Moreover, a flight to profitable stocks by safety-first investors is unlikely to drain the pool of would-be investors in the milestone stories.

Rael Mazansky, a vice president at Credit Suisse First Boston, noted that big cap biotechs and development stage plays have different investor bases. "When investors in the latter get risk averse in biotech, I think they either sit on cash or go short. It doesn't mean that they'll invest in Genzyme."

Indeed, Credit Suisse First Boston Managing Director Pete Meyers sees a growing investor base for companies coming up on Phase II data, "especially if the company can follow up with Phase III data in 12-18 months."

A case in point is AtheroGenics Inc., which went up 40% last week after announcing that its AGI-1067 met the primary endpoint in the Phase IIb CART-2 trial in an interim analysis in patients with

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coronary artery disease (CAD) *(see "How CART Changed its Horse," A15).*

In the fourth quarter, milestones in the Phase II space include a pair of data events for Amylin Pharmaceuticals Inc. (AMLN, San Diego, Calif.). These include data for exenatide LAR to treat Type II diabetes. The compound, a long-acting release (LAR) formulation of synthetic exendin-4, is partnered with Eli Lilly and Co. (LLY, Indianapolis, Ind.) and uses delivery technology from Alkermes Inc. (ALKS, Cambridge, Mass.).

AMLN also expects to report data for its AC137 synthetic amylin analog to treat obesity.

Still, Deutsche Bank's Cohen cautioned that many companies in Phase II testing may find it challenging to attract investor attention unless they are seen as bargains. "There is a bifurcation in investor interest in commercial companies versus science companies. Interest in the former is becoming more pronounced," he said. "Thus, investors will be more reluctant over time to invest in non-revenue producing companies unless there's a compelling valuation."

The IPO front

There were only six U.S. IPOs in the third quarter, down from 12 in the second quarter and nine in the first quarter. But while haircuts are still in style — four of the six IPOs in the third quarter sold shares below their proposed price ranges — the aftermarket performances of these companies have been relatively strong. Only one of the IPOs — in vivo imaging company Xenogen Corp. (XGEN, Alameda, Calif.) — is under water, and not by much. XGEN sold its shares at $7 and is down 11% to $6.20 *(see "U.S. IPO Performance").*

Opinions diverge on whether the IPO window will be open in the fourth quarter for the 14 companies still in the queue. One camp of VCs, bankers and buysiders thinks the window is closed until 2005, while the other camp expects that a few IPOs can get out.

While the third quarter IPOs have done well, about half of the 34 companies that have gone public since the current window began last October are under water.

Alex Zisson, a venture partner at Thomas, McNerney & Partners, is in the former group. "There's no evidence that the window will open before the election," he said. "I assume the IPO market is in a holding period before 2005."

Chris Ehrlich, a partner at InterWest Partners, agreed. Although he expects some companies to join the queue, "we think there's not going to be a lot of biotech IPO activity until January. The vast majority of bankers we talk to say 'January'."

But Domain's Nicole Vitullo, who manages the firm's public equity portfolio, thinks that "there's still some life in the IPO window, although it will take a late stage story to get a deal done. If there is life, companies will want to be in the queue, so I expect to see some new filings as well."

MPM's von Emster is taking a wait-and-see attitude and is looking to see whether an IPO from Theravance Inc.

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U.S. IPO performance

Third quarter IPOs fared well. Only one is below water. Overall, 16 of the 34 U.S. IPOs this window are below water. Mcap in millions

Company	Date	Price	Mcap	9/30 price	9/30mcap	Price chg
Acusphere (ACUS)	10/8/03	$14.00	$199.8	$6.26	$107.7	-55%
Advancis (AVNC)	10/17/03	$10.00	$226.9	$8.15	$184.9	-19%
Myogen (MYOG)	10/29/03	$14.00	$359.2	$8.10	$207.8	-53%
CancerVax (CNVX)	10/29/03	$12.00	$320.4	$8.10	$216.1	-33%
Genitope (GTOP)	10/30/03	$9.00	$166.7	$9.87	$236.8	10%
NitroMed (NTMD)	11/6/03	$11.00	$279.4	$23.84	$612.6	117%
Pharmion (PHRM)	11/6/03	$14.00	$335.0	$51.70	$1,580.9	269%
Eyetech (EYET)	1/29/04	$21.00	$831.6	$33.99	$1,372.8	62%
GTx (GTXI)	2/2/04	$14.50	$356.7	$11.66	$287.5	-20%
Renovis (RNVS)	2/5/04	$12.00	$283.6	$8.01	$193.6	-33%
Corgentech (CGTK)	2/11/04	$16.00	$417.6	$17.07	$466.0	7%
Dynavax (DVAX)	2/18/04	$7.50	$184.3	$5.44	$133.8	-27%
Xcyte (XCYT)	3/16/04	$8.00	$116.8	$3.17	$46.9	-60%
Tercica (TRCA)	3/16/04	$9.00	$212.0	$9.00	$214.7	0%
Anadys (ANDS)	3/25/04	$7.00	$155.0	$5.30	$117.1	-24%
Santarus (SNTS)	3/31/04	$9.00	$254.9	$9.07	$328.3	1%
Memory (MEMY)	4/5/04	$7.00	$141.5	$7.66	$155.9	9%
Corcept (CORT)	4/14/04	$12.00	$271.7	$7.84	$177.5	-35%
Immunicon (IMMC)	4/15/04	$8.00	$182.7	$10.00	$228.4	25%
Barrier (BTRX)	4/28/04	$15.00	$326.9	$12.16	$242.7	-19%
Cytokinetics (CYTK)	4/29/04	$13.00	$363.2	$13.30	$371.6	2%
Critical Therap (CRTX)	5/26/04	$7.00	$167.3	$5.85	$139.8	-16%
Acadia (ACAD)	5/26/04	$7.00	$117.5	$7.80	$130.9	11%
Alnylam (ALNY)	5/27/04	$6.00	$120.2	$5.76	$115.4	-4%
Inhibitex (INHX)	6/3/04	$7.00	$126.2	$6.35	$114.5	-9%
Metabasis (MBRX)	6/16/04	$7.00	$125.1	$5.82	$104.0	-17%
Momenta (MNTA)	6/21/04	$6.50	$159.7	$8.23	$202.2	27%
Senomyx (SNMX)	6/21/04	$6.00	$148.1	$9.00	$222.1	50%
Phase Forward (PFWD)	7/15/04	$7.50	$240.3	$8.26	$264.7	10%
Xenogen (XGEN)	7/16/04	$7.00	$102.7	$6.20	$91.0	-11%
Idenix (IDIX)	7/21/04	$14.00	$669.2	$16.00	$764.8	14%
Auxilium (AUXL)	7/23/04	$7.50	$154.4	$8.53	$175.6	14%
MannKind (MNKD)	7/28/04	$14.00	$453.5	$20.04	$649.2	43%
New River (NRPH)	8/5/04	$8.00	$142.1	$9.90	$175.8	24%

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(South San Francisco, Calif.) could reopen the gates. The company hopes to sell 5.2 million shares at $13-$15. A sale at $14 would raise $72.8 million and value Theravance at $714 million.

The small molecule therapeutic developer has multiple clinical compounds, including two asthma products that have completed Phase IIa studies and an antibiotic in Phase II testing. Theravance also has a broad relationship with Glaxo-SmithKline plc (LSE:GSK; GSK, London, U.K.) *(see BioCentury, April 5).*

Last week, two more companies filed to go public. Cardiovascular play CardioVascular BioTherapeutics Inc. (Henderson, Nev.) filed to raise $20 million in an IPO through the sale of 2 million shares at $10. MediciNova Inc. (San Diego, Calif.) hopes to go out on the Tokyo Stock Exchange's market of the high-growth and emerging stocks (MOTHERS). The specialty pharma company filed to raise up to $100 million *(see B17).*

IPO queue

The IPO queue now stands at 14 companies. Many investors are looking to Theravance to restart the window. The small molecule developer could price as early as this week. (A) The compound is marketed in Germany, but in the U.S., where Salmedix has rights, it's in Phase II

Company	Date filed	Proposed shares	To be raised (M)	Price range	Shares after offering	Clinical status
Adeza	8/6/04	TBD	Up to $69	TBD	TBD	Mkt
Celldex	4/9/04	TBD	Up to $50	TBD	TBD	Ph I
Corus	8/27/04	TBD	Up to $100	TBD	TBD	Ph II
CoTherix	3/11/04	5M	$45.0	$8-$10	19.3M	NDA
Favrille	4/8/04	TBD	Up to $86.3	TBD	TBD	Ph III
Icagen	4/8/04	TBD	Up to $86.3	TBD	TBD	Ph II
Salmedix	4/23/04	TBD	$86.3	TBD	TBD	Ph II (A)
Targacept	5/14/04	TBD	Up to $86.3	TBD	TBD	Ph II
Theravance	6/10/04	5.2M	$72.8	$13-$15	51M	Ph II
Threshold	4/9/04	TBD	Up to $86.3	TBD	TBD	Ph III
ViaCell	4/6/04	TBD	Up to $92	TBD	TBD	Ph I/II
BioNumerik	6/9/04	TBD	Up to $86.3	TBD	TBD	Ph III
CardioVascular	9/27/04	2M	$20.0	$10	TBD	Ph I/II
MediciNova	10/1/04	TBD	Up to $100	TBD	TBD	Ph I

On the outs

Another interesting dynamic will be the behavior of the companies in the class of 2004 IPOs that didn't raise enough money because they had to take haircuts. A number of these now need to go back to investors to top up. Of the 21 loss-making companies that took haircuts this window, six have less than a two years of cash *(see "Got Cash?" A6).*

JMP's Kerry said that about 15 companies that did IPOs in this window are planning financings. The problem, he said, is that these companies typically "are managing a stock price that's under their IPO price and have capital that's underneath the comfort zone." He did say that many have interesting catalysts in the not-too-distant future and that milestones will help get deals done.

OrbiMed's Borho said that PIPEs would be an important financing vehicle for such companies. "You can get good terms on these as an investor," he said. "That's a way I'd like to get the shares."

In addition, Borho said he'll keep his eye on lockup expirations as a potential entry point into the IPO crop. "Rather than buy the new issue, I'd rather get it on lockup. I don't want to be caught offsides by the VCs."

The problem with this approach, he said, is that "VCs are not sitting on big returns so they're not interested in distributing shares — they don't want to lock in 1.5x returns. So the stocks are cheap, but the VCs aren't distributing."

Grimaldi predicted that PIPEs and registered direct financings will be used by companies valued below $300 million — a group that includes 26 of the 34 companies that had IPOs this window. "Follow-ons will be an instrument for companies valued above $400 million," she said.

Indeed, on the last day of the third quarter, infectious disease play Vicuron Pharmaceuticals Inc. (MICU; NMerc:MICU, King of Prussia, Penn.) raised $70.8 million in a follow-on through the sale of 4.8 million shares at $14.75. MICU closed Friday with a market cap of $809.4 million.

Last month, MICU said it plans to amend its NDA for anidulafungin to treat esophageal candidiasis in the second quarter of 2005. The company said it could receive approval in the fourth quarter of next year. In a May approvable letter for the compound, FDA asked for additional data.

MICU also said it expects to submit a separate NDA for the compound to treat invasive candidiasis in the third quarter of 2005.

This leaves two U.S. deals filed in the waning weeks of the third quarter: OSI Pharmaceuticals Inc. (OSIP, Melville, N.Y.) and Pain Therapeutics Inc. (PTIE, South San Francisco, Calif.).

OSIP is hoping to sell 5.5 million shares through Merrill Lynch; Morgan Stanley; Banc of America Securities; Bear, Stearns; and Lazard. OSIP's Tarceva erlotinib, a small molecule oral EGFR inhibitor partnered with Genentech Inc. (DNA, South San Francisco, Calif.) and Roche (SWX:ROCZ, Basel, Switzerland), is under FDA and EU review to treat non-small cell lung cancer (NSCLC). OSIP's market cap is $2.8 billion.

PTIE plans to sell 8 million shares through Citigroup Global Markets; UBS Securities; CIBC World Markets; and Rodman & Renshaw. Although the company's market cap is $256.5 million, PTIE does have a near term driver. In the first quarter, the company expects data from a Phase III trial of its Oxytrex combination of immediate-release oxycodone and low-dose naltrexone to treat low back pain.

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Got cash?

Of the 21 IPOs in this window that took haircuts, six look to have less than two years of cash based on their loss for the first half of 2004. (A) Net loss figure used; (B) Santarus raised money in July; Cash, operating loss and imputed loss in millions

Company	IPO date	6/30 cash	1H04 oper loss	Imputed FY04 loss	Imputed yrs of cash	Milestone
Advancis (AVNC)	10/17/03	$41.2	$19.5	$39.0	1.1	Start Ph III (Oct.)
Renovis (RNVS)	2/5/04	$103.1	$18.9	$37.8	2.7	DSMB review of Ph III trial (4Q04)
Dynavax (DVAX)	2/18/04	$74.0	$7.1	$14.2	5.2	Ph II/III data (early '05)
Tercica (TRCA) (A)	3/16/04	$69.0	$19.1	$38.2	1.8	Submit NDA (early '05)
Xcyte (XCYT)	3/16/04	$33.7	$11.9	$23.8	1.4	NA
Anadys (ANDS)	3/25/04	$42.3	$18.4	$36.8	1.1	Interim Ph II data (year end)
Santarus (SNTS) (A) (B)	3/31/04	$82.0	$27.0	$54.0	1.5	Drug launch (4Q04)
Memory (MEMY)	4/5/04	$54.2	$10.7	$21.4	2.5	NA
Corcept (CORT) (A)	4/14/04	$52.0	$6.1	$12.2	4.3	Ph III data (1H06)
Immunicon (IMMC)	4/15/04	$67.6	$13.6	$27.2	2.5	Seek label extension for cancer test (2005)
Acadia (ACAD)	5/26/04	$48.8	$12.3	$24.6	2.0	NA
Critical Therap (CRTX)	5/26/04	$92.3	$13.6	$27.2	3.4	Drug launch (mid-'05)
Alnylam (ALNY)	5/27/04	$46.1	$20.3	$40.6	1.1	Enter clinic ('05)
Inhibitex (INHX)	6/3/04	$47.9	$11.7	$23.4	2.0	Complete Ph III enrollment (late '05)
Metabasis (MBRX)	6/16/04	$51.4	$4.2	$8.4	6.1	Start Ph III ('05)
Momenta (MNTA)	6/21/04	$64.0	$5.6	$11.2	5.7	Submit ANDA ('05)
Senomyx (SNMX)	6/21/04	$44.4	$8.5	$17.0	2.6	NA
Phase Forward (PFWD)	7/15/04	$19.0	NA	NA	NA	NA
Xenogen (XGEN)	7/16/04	$5.4	$11.4	NA	NA	NA
Auxilium (AUXL)	7/23/04	$20.9	NA	NA	NA	NA
New River (NRPH)	8/5/04	$2.1	NA	NA	NA	Start pivotal trials (4Q04)

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VC valuations

Because of the low valuations of many companies that went public in this window, it's also possible that those VCs whose charters allow it might put their money to work in small public companies.

"We've talked with VCs who are looking at public companies," said CSFB's Mazansky. "There are newly public biotechs that are finding themselves in no-man's land — a market cap around $100 million and low stock prices. These companies are right in the wheelhouse of VCs – if you have a Phase III company with a sub-$100 million value, that's quite compelling."

VCs did just that with cardiovascular play Myogen Inc. (MYOG, Denver, Colo.), which ended the quarter with a $207.8 million market cap. In late September, the company raised $60 million in a private placement through the sale of 9.2 million shares at $6.53. Investors included existing stockholders New Enterprise Associates; InterWest Partners; Perseus-Soros Biopharmaceutical Fund; and Sequel Venture Partners.

MYOG was one of the first companies to go out in the IPO window — it raised $70 million on Oct. 29, 2003, through the sale of 5 million shares at $14. MYOG's post-money valuation was $359.8 million.

The company markets Perfan I.V. intravenous enoximone to treat acute decompensated heart failure in Europe. The company's oral formulation of enoximone, a phosphodiesterase-3 (PDE-3) inhibitor, is in two Phase III trials for advanced chronic heart failure — ESSENTIAL I and II. Earlier this year, the compound missed the primary endpoint in MYOG's Phase III EMOTE trial.

The company hopes to report preliminary top-line results from ESSENTIAL I and II in mid-2005.

MYOG's other Phase III compound is ambrisentan, a selective endothelin A receptor antagonist to treat pulmonary arterial hypertension. The company hopes to complete enrollment in the ARIES 1 and 2 Phase III trials in the second quarter of 2005.

Europe's news flow

Selected fourth quarter milestones in Europe.

Company	Product	Indication	Milestone
Actelion (SWX:ATLN)	Tracleer	Pulmonary arterial hypertension (PAH)	Interim results of Pfizer's PAH Ph II/III trial of sildenafil, which could compete with Tracleer
Actelion (SWX:ATLN)	Veletri	Acute heart failure	Second interim analysis of Ph III VERITAS 1 and 2 trials; final results expected spring 2005
Alizyme (LSE:AZM)	ALT-962	Obesity	Global (ex-Japan) partnership
Ark (LSE:AKT)	EG005	Lipodystrophy syndrome in HIV patients	Ph II data
Pharmagene (LSE:PGN)	PGN0052	Cystic fibrosis	Ph II data
Serono (SWX:SEO; SRA)	Raptiva	Chronic plaque psoriasis	EU launch
Shire (LSE:SHP; SHPGY)	Fosrenol	End-stage renal disease	Late October PDUFA date

4Q Financial Markets Preview

Europe: The news will be light

By Shaun Brown
Senior Writer

The public markets in Europe look to be volatile through the end of the year, but biotech investors have not simply fled to profitable or revenue-generating companies, as have generalist investors. Instead, the specialists have taken a blended approach of both defensive investing in profitable and late-stage companies and stock-picking on low valuations. The problem for Europe is that there are few milestones for investors to hang their hats on this quarter, leaving them to focus on long-term fundamentals.

"We've seen defensive investing on the part of generalists with concerns over oil prices, terrorist attacks and Iraq," said Gareth Powell, healthcare fund manager at Framlington Investment Managers. With generalists out of the picture, the specialists have had pretty much of an open field. Specialists have been "picking up stocks, because they were looking very cheap, especially when the NBI was below 650 in late July and August," said Powell, referring to the NASDAQ Biotech Index.

The European sector had a relatively quiet third quarter, with the BioCentury London Index gaining 1%, while the BioCentury Europe Index lost 1%. Both remain up on the year: 16% for the London group and 17% for the continental benchmark *(see "London vs Europe," A10).*

"As in other sectors there has been a flight to quality and conservatism by investors and a reduction in risk appetite," said Ed Burke, fund manager at Invesco Perpetual. Still, he said, "I think there are interesting money-making opportunities in the biotech area."

At the same time, there are signs that private companies and their investors are beginning to adapt to the unrelenting public investor demands for bigger, stronger companies.

News flow

For European companies, news flow through the end of the year is light, at best, with only a few companies expected to put out significant clinical and regulatory news. "There is some news flow around, medical meetings will drive the news flow, but there's nothing significant," Powell noted *(see "Europe's News Flow").*

Other investors are looking for corporate news to push the markets over the next six to 12 months. "The main driver for Europe is going to be corporate activity from both the private and public sector," said Michael Bourne of Reabourne Technology Investment Management.

For instance, investors are watching antibody specialist Cambridge Antibody Technology Group plc (LSE:CAT; CATG, Cambridge, U.K.) in anticipation of its upcoming legal proceeding against Abbott Laboratories (ABT, Abbott Park, Ill.) over the level of Humira adalimumab royalties. That trial in London is due to begin in November.

"CAT is cheap now and the risk-reward is good if the Abbott court case works out for them, relative to the down side," Powell said.

Among other companies mentioned by investors as good investment opportunities, cardiovascular company Actelion Ltd. (SWX:ATLN, Allschwil, Switzerland) continues to top the list, as it is considered to be one of Europe's few safe stocks.

Other names tipped by market watchers include drug delivery play SkyePharma plc (LSE:SKP; SKYE, London, U.K.). Investors have been waiting all year for SKP to sign a deal for its "pulmonary package," which includes Flutiform, a fixed-dose combination inhaled steroid/long-acting beta-agonist bronchodilator.

Last January, SKP said it was in negotiations for three deals that had previously been expected in 2003 *(see Ebb & Flow, Jan. 12).* By September, the company had signed two: with Medeus Pharma Ltd. (Stevenage, U.K.) for EU rights to market SKP's DepoMorphine sustained-release morphine to control moderate to severe post-operative pain, and with Trigenesis Therapeutics

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Inc. (Plymouth Meeting, Penn.) which received residual rights in unlicensed territories to three of SKP's marketed products, and rights to six compounds in development and six dermatology delivery technologies. In May, Trigenesis was acquired by Dr. Reddy's Laboratories Ltd. (RDY, Hyderabad, India) *(see BioCentury, May 10).*

But the most anticipated deal, for three pulmonary compounds, has yet to be announced. In September, SKP said it was in due diligence with several potential partners.

Also on the deal front, scuttlebutt in Europe is that antibody play Crucell N.V. (Euronext:CRXL; CRXL, Leiden, the Netherlands) will soon sign yet another pharma partner for its PER.C6 cell line technology. CRL signed two similar deals in August, with Wyeth (WYE, Madison, N.J.) and GlaxoSmithKline plc (LSE:GSK; GSK), London, U.K.) *(see BioCentury, Aug. 30 & Aug. 23).*

Among the handful of clinical events before year end, investors are expecting metabolic, cancer and cardiovascular company Ark Therapeutics Ltd. (LSE:AKT, London, U.K.) to release Phase II results for its EG005 mitochondria stimulator of angiotensin II to treat lipodystrophy syndrome in HIV patients.

Investors are also interested in Protherics plc (LSE:PTI, London, U.K.), which turned its first profit earlier this year from sales of its CroFab sheep polyclonal antibody to treat rattlesnake bites and DigiFab sheep polyclonal antibody to treat digoxin toxicity *(see BioCentury, May 31).* PTI is running Phase I trials using two new formulations of its Angiotensin vaccine that incorporate undisclosed adjuvants that potentially can improve the immune response to the vaccine. The original Phase II formulation has been dropped and the Phase I results are expected by year end.

Longer term, investors also mention GPC Biotech AG (FSE:GPC; GPCB, Munich, Germany), which expects to begin a Phase I/II study this quarter of its satraplatin in combination with taxotere to treat cancer. The compound has been in Phase III trials as a second-line therapy for hormone-refractory prostate cancer (HRPC) since 2003. Those data are not expected until 2006.

Follow-ons

While the $186.9 million raised in seven European follow-ons this year is more than was raised in the same nine months in the last two years, investors expect follow-on activity to be light for the foreseeable future, as the markets remain uncertain and most public companies are reasonably well funded.

In 2003, 11 European companies raised $406.8 million in follow-on financings, which included Elan Corp. plc (ELN) raising $173.3 million.

"I think people that believe in certain stories will back the company, whatever the market conditions, but the dilutions will be pretty big," said Powell. "The benefit now is the sector is very well capitalized because of the strength of last year."

IPO pushing VCs

The most interesting changes in Europe are going on among private companies. With all three of Europe's 2004 IPOs trading under water, the push for VCs to develop stronger IPO candidates is causing a shift in priorities.

> ***'Good stories will get money; bad stories are being liquidated.'***
>
> **— HBM's Andreas Wicki**

"The spotlight on partnerships is higher than ever right now in terms of the capital market's viewpoint," said John Goodey, who heads European biotech corporate banking at Deutsche Bank. "This is unlikely to change in the next couple of quarters. The attitude of investors right now is to reduce risk rather than looking for the high octane stories. Investors are wanting more Phase II or Phase III companies."

Indeed, the few companies that are preparing to go public all have products at least in later stage clinical development and partnerships with big biotech or pharma. The most optimistic view is that one or two companies could get out by year end if the markets turn up *(see "Europe's Potential IPOs").*

Companies in the private group thus are busy doing deals, whether partnerships or mergers and acquisitions. In August, Orexo AB (Uppsala, Sweden) granted Endo Pharmaceuticals Inc. (ENDP, Chadds Ford, Penn.) North American rights to develop and market Rapinyl sublingual mucoadhesive fentanyl for breakthrough cancer pain. Rapinyl is in Phase II trials and ENDP expects to start Phase III studies in 2005 *(see BioCentury, Aug. 23).*

In July, Paion GmbH (Aachen, Germany) granted North American development and marketing rights for its desmoteplase to treat stroke to Forest Laboratories Inc. (FRX, New York, N.Y.). Desmoteplase, a plasminogen activator, is scheduled to enter Phase IIb/III trials this year in acute ischemic stroke *(see BioCentury, July 12).*

Given that platform companies and product companies without revenues have little chance to go public, VCs also are starting to merge companies in their portfolios as a way to get them ready for market.

"I think the VC industry is going to have to hang on to companies for a lot longer than in the past and that companies will have to be significantly more advanced in terms of breadth and depth of pipeline," said Burke, who sees a lot of M&A potential in the private group.

One such deal was to be announced today. Pulmonary and respiratory company Etiologics Ltd. (Slough, U.K.) was expected to announce a merger with drug discovery play Argenta Discov-

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Europe's potential IPOs

Selected companies mentioned by bankers and investors as IPO possibilities. (A) Formed by merger between ProSkelia and Strakan

Company	Status	Selected partners
Ardana	Mkt	Columbia Labs; Senetek
Arpida	Ph II	Roche
BioXell	Ph IIa done	Roche
IDEA	Ph III	Undisclosed partner
Intercell	Ph II	Sanofi-Aventis
Jerini	Ph III	Baxter; Merck
Newron	Ph III	Zambon
Orexo	Ph II done	Endo Pharma
ProStrakan (A)	Mkt	Genentech; Sanofi-Aventis

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ery Ltd. (Harlow, U.K.). The merged company will have over four preclinical programs in respiratory and inflammation indications, including a chronic obstructive pulmonary disease (COPD) program from Etiologics. Argenta brings chemistry and biology drug discovery.

The merged company will have revenues of about £11 million ($19.8 million) a year from Argenta's hit-to-lead and lead optimization services and Etiologics' in vivo and in vitro respiratory disease models. The new company will have about £9 million ($16 million) in cash, enough for at least three years. Etiologics and Argenta share one investor: MVM.

"This is an aggressive and proactive strategy to get position for IPOs," said Helmut Schuehsler of TVM Techno Venture Management. "We will take advantage of the companies that do not have the money to work through there own strategies. This is a strategy that can yield bigger companies with more critical mass. If there is anything missing in the pipeline, we can fill it up either by in-licensing or acquisition."

Schuehsler hopes this will make DeveloGen AG (Goettingen, Germany) an attractive IPO candidate when the window opens in Germany.

DeveloGen, a Global Life Science Ventures portfolio company**,** last year acquired Peptor Ltd., a TVM company. The deal combined DeveloGen's platforms, which are based on stem cell regeneration and phenotype screens for targets in diabetes, obesity and metabolic syndrome, with Peptor's clinical pipeline *(see BioCentury, Nov. 17, 2003).*

The lead compound is DiaPep277, a peptide analog of an HSP-60 epitope in Phase II studies to treat Type I diabetes and latent autoimmune diabetes in adults. DiaPep277 is partnered with Sanofi-Aventis S.A. (Euronext:SAN; SNY, Paris, France) and is expected to enter Phase III next year.

In May, DeveloGen raised €19 million ($22.6 million) in a series C round led by TVM. The company now has about three years of runway,

Bert van Toor of GLSV expects to see not only VC-driven mergers, but company-led M&A as well. "Small companies with good management will be looking to develop themselves in this way," he said.

For example, French musculoskeletal play ProSkelia SA and U.K. drug delivery company Strakan Group Ltd. in September completed their merger to form the Prostrakan Group Ltd. (Galashiels, U.K.). The newco has four marketed products and 19 clinical and preclinical projects *(see BioCentury, Sept. 13).* CEO Wilson Totten told BioCentury this was a company-driven deal.

Another recently completed company-driven merger was between functional genomics and metabolic company Graffinity Pharmaceuticals AG (Heidelberg, Germany) and musculoskeletal and metabolic company MyoContract AG (Liestal, Switzerland) to form Santhera AG *(see BioCentury, Sept. 13).* Santhera now has a fee-for-service drug fragment-based discovery platform and an undisclosed compound due to enter Phase III studies by early next year, plus two preclinical programs.

As a result of these sorts of moves, the smart money in the private sector is seeing the glass in Europe as half-full for the first time in several years.

"There is plenty of money that needs to find a home, so I would not say there is a defensive environment," said HBM CEO Andreas Wicki. "Good stories will get money; bad stories are being liquidated."

'The spotlight on partnerships is higher than ever right now in terms of the capital market's viewpoint.'

— Deutche Bank's John Goodey

Results by market cap

Until the third quarter, the big cap band of biotechs had shown gains every quarter since the fourth quarter of 2002. It was the only group among both biotechs and the broader markets to do so.

	4Q02	1Q03	2Q03	3Q03	4Q03	1Q04	2Q04	3Q04	FY02	FY03
≥$2B	9%	5%	25%	6%	6%	7%	6%	-8%	-52%	51%
$1-$1.9B	-4%	-7%	21%	22%	8%	14%	0%	-11%	-49%	42%
$500M-$999M	9%	-1%	33%	7%	9%	5%	-3%	-12%	-43%	52%
$200M-$499M	9%	-9%	32%	11%	6%	5%	-5%	-6%	-51%	40%
<$200M	14%	-5%	57%	22%	8%	18%	-9%	-4%	-50%	99%
NASDAQ	14%	0%	21%	10%	12%	0%	3%	-7%	-32%	50%
DJIA	10%	-4%	12%	3%	13%	-1%	1%	-3%	-17%	25%

3Q Wrap-Up

Few drivers

One lesson to take away from last quarter is that investors will not interrupt a summer vacation if the news flow is light. Indeed, there was just a smattering of positive product approval news last quarter. Moreover, the third quarter snapped a streak of six consecutive quarters where good news outnumbered bad news events *(see 3Q Approvals & Setbacks, A11).*

Of the slim number of approvals, perhaps the most significant was Truvada from Gilead Sciences Inc. (GILD, Foster City, Calif.). The HIV drug is a once-daily combination of GILD's Emtriva emtricitabine and its Viread tenofovir. MPM's Kurt von Emster noted that "the Truvada launch hasn't adversely affected sales of Viread so far. It was possible that there would be cannibalization, but it hasn't happened yet. The way the HIV market is expanding, this looks good" for GILD.

The dearth of inflection points likely contributed to an 8% decline in the BioCentury 100 Index last quarter, which was larger than the drops seen in the broad market indices *(see "Index Performance").* The selling was across the board, as all market cap bands were down on the quarter *(see "Results by Market Cap").*

On the year, it appears that investors are moving to the poles — the group of 24 biotechs with market caps of at least $2 billion is up 5% and the group below $200 million group is up 3%. Those sandwiched in between are in the red.

The picture for European biotech was brighter, as the 1% uptick by the BioCentury London Index and the 1% drop on the BioCentury Europe Index sat atop the general markets. The two European benchmarks also are out front, with gains of 16% for the London group and 17% for the basket of continental names on the year.

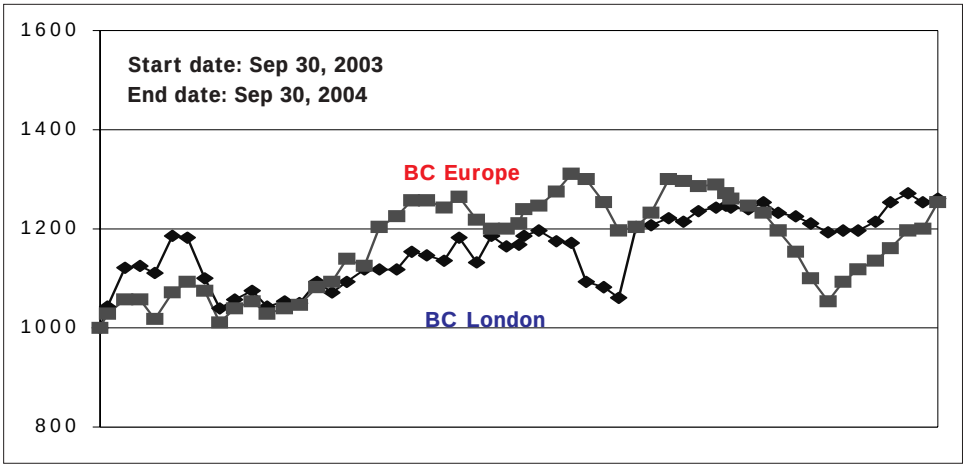
Index performance

Despite posting one of the larger losses in the third quarter, the biotech group is still the biggest gainer since the start of the biotech bull on March 7, 2003.

	1H04	3Q	YTD	Since 3/7/03
BC Europe	18%	-1%	17%	138%
BC 100	10%	-8%	2%	59%
BC London	15%	1%	16%	53%
NASDAQ	2%	-7%	-5%	42%
S&P 500	3%	-2%	0%	33%
DJ 30	0%	-3%	-4%	29%
AMEX Pharma	-3%	-5%	-8%	9%

London vs Europe

The BioCentury London Index, which consists of 14 companies, gained 1% in the third quarter after rising 7% in the second quarter. The BioCentury Europe Index, which consists of 19 continental biotech stocks, fell 1% in the third quarter after increasing 5% in the second quarter. In the last 12 months, the London and European indices are up 26% and 25%, respectively.



3Q approvals

Selected third quarter product approvals.

Company	Approval
Cellegy (CLGY)	U.K. approves Rectogesic (Cellegesic) to treat pain associated with chronic anal fissures
Forest (FRX)	FDA approves Campral acamprosate to treat alcohol dependence
Gilead (GILD)	FDA approves HIV drug Truvada, a once-daily combination of Emtriva emtricitabine and Viread tenofovir
Medicines Co. (MDCO)	EU approves Angiox (Angiomax) anticoagulant for use in patients undergoing percutaneous coronary interventions
Palatin (PTN)	FDA approves NeutroSpec (formerly LeuTech), a radiolabeled monoclonal antibody that binds white blood cells, to diagnose appendicitis in patients with equivocal symptoms
PhotoCure (OSE:PHO)	FDA approves Metvix topical photodynamic therapy (PDT) to treat actinic keratosis
Provalis (LSE:PRO; PVLS)	FDA approves in2it automated diagnostic platform and HbA1c test for monitoring diabetes

3Q setbacks

Selected third quarter product setbacks.

Company	Setback
Allergan (AGN)	Receives FDA not approvable letter for Tazoral oral tazarotene to treat moderate to severe psoriasis
Forest (FRX)	Neramexane plus acetylcholinesterase (AChE) inhibitors fails Phase III to treat moderate to severe Alzheimer's disease (AD)
IntraBiotics (IBPI)	Discontinues development of iseganan for all indications, including to prevent ventilator-associated pneumonia (VAP) and oral mucositis in radiotherapy and chemotherapy patients
Maxim (MAXM)	Ceplene plus interleukin-2 (IL-2) fails Phase III to treat advanced malignant melanoma patients with liver metastases
Merck (MRK)	Pulls arthritis drug Vioxx rofecoxib from markets worldwide after long-term studies showed increased risk of myocardial infarction and stroke
Miravant (MRVT)	Receives FDA approvable letter for SnET2 photodynamic therapy to treat wet age-related macular degeneration (AMD) in which the agency requested a confirmatory trial
Oscient (OSCI)	Discontinues Phase III testing of Ramoplanin to prevent vancomycin-resistant enterococci bloodstream infections

Strategy

Checking out new books from the library

Exelixis Pharmaceuticals Inc.'s genomics-based discovery efforts historically have been focused on kinases. With the planned acquisition of X-Ceptor Therapeutics Inc., EXEL is branching out into nuclear hormone receptors. The company thinks it will be able to make the jump because its existing compound library has been shown to contain hits against NHRs.

EXEL has been using its library of about 4 million compounds to develop small molecules against kinase targets. These efforts have been productive, as EXEL (South San Francisco, Calif.) has three compounds in the clinic and hopes to file about two INDs per year going forward.

"Over the past year we screened against GPCRs and nuclear hormone receptors. We wanted to see how good our library would be for those targets," said President and CEO George Scangos. "From the screens, we identified many compounds and are now convinced that the library is good for these areas."

He noted that the NHR space is "chemically easy to enter but has incredibly complicated biology."

NHRs are ligand-activated transcription factors. They regulate gene expression and are involved in endocrine signaling. In addition, these receptors have ligand-dependent interactions with proteins that serve as co-activators or co-repressors. As a result, NHRs give tissue-selective gene regulation.

That's where X-Ceptor (San Diego, Calif.) comes in. The company, which was founded in 1999, is focused on small molecules that modulate NHRs. EXEL will pay $2.9 million in cash and issue 2.5 million shares in the deal. Using EXEL's Friday close of $8.60, the stock portion is valued at $21.5 million and the total deal value is $24.4 million.

X-Ceptor's NHR programs are "very sophisticated," according to Scangos. "They've been able to de-orphanize receptors. As the biology of more nuclear hormone receptors is understood, the interest in the field increases. The therapeutic potential of modulating these targets is only beginning to be tapped."

X-Ceptor's most advanced preclinical projects target liver X receptor, farnesoid X receptor and mineralocorticoid receptor.

The liver X receptor program is partnered with Sankyo Co. Ltd. (Tokyo, Japan) and is intended to treat cholesterol disorders. X-Ceptor's compounds against farnesoid X receptor are expected to treat hypertriglyceridemia in patients with Type II diabetes, metabolic syndrome and related metabolic disorders. Finally, the mineralocorticoid receptor therapeutics are to treat hypertension and other cardiovascular disorders.

EXEL expects to file INDs for certain of these programs in 2006.

EXEL's most advanced compounds are for cancer, but Scangos noted that X-Ceptor's compounds for metabolic and cardiovascular diseases are "not a move into new areas. We've had metabolic disease targets and screens and have a compelling program here. We also have cardiovascular programs. The acquisition will accelerate those programs." — *Steve Edelson*

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Product Development

Deconstructing the COX-2 difference

By Christopher Maggos & Susan Schaeffer Staff Writers

Now that Merck & Co. Inc. has pulled its Vioxx rofecoxib COX-2 inhibitor from the market for safety reasons, the big question is whether all COX-2 inhibitors will face the same problem. There are three important differences that could make some COX-2 inhibitors safer than others: the degree of selectivity for COX-2, pharmacology and half-life.

MRK (Whitehouse Station, N.J.) pulled Vioxx after an independent data safety monitoring committee for the APPROVe trial said that compared to placebo, Vioxx 25 mg doubled the risk of cardiovascular events such as myocardial infarction or stroke after 18 months of treatment. APPROVe (Adenomatous Polyp Prevention on Vioxx) was a 2,600-patient trial started in 2000 to test the ability of Vioxx to prevent recurrence of colorectal polyps in patients with a history of colorectal adenomas.

MRK said that 7.5 patients per 1000 patients (0.75%) receiving placebo had a confirmed cardiovascular event compared to 15 patients per 1000 (1.5%) given Vioxx.

MRK and FDA said in conference calls that there is not enough evidence to say whether an increased risk of cardiovascular events also may be associated with other COX-2 inhibitors. FDA said it will be interested in seeing more long-term data on COX-2 inhibitors that are on the market and in development. The agency said it had not yet decided whether it would add warnings to other COX-2 inhibitors or what kinds of long-term studies it could require.

There are five COX-2 inhibitors still on the market in the U.S. or Europe for a variety of indications: Arcoxia etoricoxib from MRK; Bextra valdecoxib, Celebrex celecoxib and Dynastat parecoxib from Pfizer Inc. (PFE, New York, N.Y.); and Mobic meloxicam from Abbott Laboratories (ABT, Abbott Park, Ill.) and Boehringer Ingelheim GmbH (Ingelheim, Germany).

Mechanistic conjecture

Cyclooxygenase (COX) is an enzyme that plays a role in the production of prostaglandins, prostacyclin and thromboxane, among other things. Prostaglandins have a variety of functions. One of the most important is that they mediate inflammation and contribute to the pathology of diseases like rheumatoid arthritis, osteoarthritis and acute conditions like post-operative pain. COX-2 inhibitors mediate their therapeutic effects by reducing production of prostaglandins.

Prostacyclin has been shown to inhibit platelet activation and act as a vasodilator. By contrast, thromboxane causes platelet activation and acts as a vasoconstrictor.

Some researchers have asserted that COX-2 mediates primarily prostacyclin while COX-1 mediates thromboxane. A paper published in *Science* in April 2002 thus suggests a yin-yang relationship between COX-1 and COX-2 enzymes that, when disrupted, could lead to negative effects.

The paper postulates that blocking only COX-2 could lead to a higher rate of cardiovascular events because it inhibits the cardioprotective effects of prostacyclin while leaving the negative actions of thromboxane unchecked.

According to the paper, "prostacyclin modulates platelet-vascular interactions in vivo and specifically limits the response to thromboxane. This interplay may help explain the adverse cardiovascular effects associated with selective COX-2 inhibitors, which, unlike aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs), inhibit prostacyclin but not thromboxane."

Indeed, one of the authors of the paper, Garret FitzGerald, told BioCentury, "If you remove the prostacyclin receptor in mice you find hardening of arteries, thrombosis and a rise in blood pressure. I think what we're seeing with Vioxx is a situation where all three

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COX-2 space

Selected compounds in late-stage development and on the market that inhibit cyclooxygenase-2 (COX-2). (A) Lead nitric oxide candidate is composed of a rofecoxib derivative

Company	Product	Indication	Status
Abbott/Boehringer	Mobic meloxicam	Osteoarthritis	Mkt
Pfizer	Bextra valdecoxib	Dysmenorrhea, osteoarthritis, rheumatoid arthritis (RA)	Mkt
Pfizer	Celebrex celecoxib	Osteoarthritis, pain, RA, familial adenomatous polyposis (FAP)	Mkt
Pfizer	Dynastat parecoxib	Post-operative pain	Submit NDA by year end; mkt'd elsewhere
Merck	Arcoxia etoricoxib (MRK-663)	Dysmenorrhea, osteoarthritis, pain, RA	Under review in U.S.; mkt'd elsewhere
Merck	Vioxx rofecoxib	Dysmenorrhea, osteoarthritis, pain, RA	Pulled from mkt
Novartis	Prexige lumiracoxib (COX189)	Osteoarthritis, pain	Ph III
Almirall	LAS 34475	Osteoarthritis	Ph II/III
GlaxoSmithKline	406381	Pain	Ph II
Merck/NitroMed	Nitrogen oxide (NO) enhancing COX-2 inhibitor (A)	Pain	Ph II (halted)

Deconstructing COX-2,
from previous page

of those things are happening." FitzGerald is chairman of the department of pharmacology at the University of Pennsylvania.

One reason why not all COX-2 inhibitors would have these side effects is that while all COX-2 inhibitors also inhibit COX-1 to some extent, their affinity for one enzyme over the other varies *(see "COX-2 Selectivity")*.

For example, the COX-2 to COX-1 binding affinity ratio is 276 for Vioxx but only 30 for Celebrex — a relative difference of about 9 times. If this selectivity turns out to be important, Celebrex could be safer because it doesn't perturb the balance of prostacyclin and thromboxane as much as does Vioxx.

But Mitch Gandelman, PFE's vice president for worldwide medical in oncology/pain and inflammation, cautioned that the "COX-2/COX-1 ratio is very hard to measure, and it depends on how you do it. Nobody really knows if that's the answer."

According to Gandelman, the reason that Celebrex and Vioxx have different cardiovascular safety profiles is not understood beyond the fact that they are different molecules — Vioxx is a sulfone and Celebrex is a sulfonamide.

"I like to think of it in terms of primary pharmacology and secondary pharmacology," he said. "They are both the same on the primary pharmacology — both are designed to inhibit COX-2 and not COX-1. But in secondary pharmacology, the drugs differ quite a bit. We don't know exactly what it's due to."

Thomas Schnitzer, assistant dean for clinical research in the rheumatology department at Northwestern University, also cautioned against jumping to conclusions. "Those affinity ratios are just numbers without real meaning. There's no good data to support that selectivity ratios are important," he said.

"What FitzGerald is hypothesizing is certainly feasible, but whether it's the actual mechanism or not we just don't know," Schnitzer said.

"One of the biggest reasons why it's not so simple is that occurrence of cardiovascular events wasn't apparent until the drug was used for a long time," he added. "I think that's an argument against such mechanistic explanations. If it were so straightforward, we should have seen these cardiovascular events a long time ago."

Schnitzer was lead author on a paper published in August in *The Lancet* looking at the gastrointestinal safety of Prexige lumiracoxib from Novartis AG (NVS; SWX:NOVN, Basel, Switzerland) compared to naproxen and ibuprofen.

Finally, another variable that could give other COX-2 inhibitors better safety profiles is their half-life, the implication being that drugs with shorter half-lives will expose patients to drug for shorter periods of time — although that could be offset if patients are dosed twice daily. Celebrex has a half-life of about 11 hours. Bextra has a half-life of 8-11 hours. Mobic's half-life is 15-20 hours. Vioxx has a half-life of about 17 hours. Dynastat's is 8 hours.

Pfizer's trials

On Friday, PFE disclosed for the first time that there are two five-year, double-blind, placebo-controlled studies of Celebrex underway. Like APPROVe, both trials are investigating whether Celebrex reduces the recurrence of pre-cancerous polyps in patients who have had polyps removed.

The first trial is a three-arm study in about 2,000 patients who are randomized to receive Celebrex 400 mg or 200 mg twice daily, or placebo. Gandelman told BioCentury that 900 patients in the trial have hit the three-year mark.

Of 1,560 patients enrolled in the second trial, 325 have reached the three-year mark, Gandelman said. Patients in that study are receiving Celebrex 400 mg once daily or placebo.

The independent data safety monitoring board that is reviewing both trials has reported no significant safety issues. The next meeting to review that trial is scheduled for the end of the month.

Gandelman said Bextra has "not been studied in as many patients" as Celebrex, and that long-term safety studies of the kind done for Celebrex are not underway. He could not say whether PFE will undertake such studies.

In a press release, Boehringer said that in a meta-analysis of 48 clinical and observational studies of 117,755 patients treated with Mobic and "traditional painkillers," there was no indication of excess risk in cardiovascular toxicity compared to non-COX-2 selective NSAIDS.

The company also said that differences in the profiles of Mobic and other selective COX-2 inhibitors are explained by structural differences and by the fact that Mobic "works by exploiting a greater degree of flexibility at the apex of the COX-2 channel."

Merck's loss, Pfizer's gain?

The demise of Vioxx is a big loss for MRK, as the patent protecting Vioxx from generic competition doesn't expire until 2013. As a result, Vioxx sales had been expected to be a substantial part of the company's bread and butter for the foreseeable future.

Vioxx, approved in 1999, posted $1.3 billion in sales in the first six months of 2004, about 9% of the company's total sales of $11.7 billion. Sales in 2003 totaled $2.5 billion. MRK last week reduced its 2004 EPS guidance by $0.50-$0.60 from its previous guidance of $3.11-$3.17.

MRK markets Arcoxia etoricoxib in many countries outside of the U.S. and still hopes to launch the drug in the U.S. next year.

Even though overall use of COX-2 inhibitors could fall on fears that the cardiovascular events are class-related, PFE will certainly be selling Celebrex or Bextra to former Vioxx users. As such, MRK's loss may be PFE's gain.

Celebrex is marketed to treat osteoarthritis, pain, RA and familial adenomatous polyposis (FAP). Already No. 2 on the market, Celebrex sales were $1.5 billion for the first half of 2004 and $1.9 billion in 2003. PFE markets Bextra to treat osteoarthritis, RA and dysmenorrhea. Bextra sales were $545 million in the first half of 2004 and $687 million in 2003.

ABT doesn't break out Mobic sales *(see "COX-2 Space," A13).*

'It's the BioCentury'™

COX-2 selectivity

Of the five compounds listed below, Prexige is the most highy selective inhibitor of cyclooxygenase-2 (COX-2). *Source: Eric Topol & Gary Falk, Comment in The Lancet*

Product	Company	COX-2:COX-1
Prexige lumiracoxib	Novartis	433:1
Arcoxia etoricoxib	Merck	344:1
Vioxx rofecoxib	Merck	276:1
Bextra valdecoxib	Pfizer	261:1
Celebrex celecoxib	Pfizer	30:1

Product Development

How CART changed its horse

By Michael Flanagan
Staff Writer

AtheroGenics Inc.'s CART-2 trial has gone through some evolutionary somersaults, and the company surprised everyone last week by disclosing preliminary rather than complete results. Nevertheless, the study adds one more piece of evidence that AGI-1067 reduces atherosclerotic plaque versus baseline. Most importantly, the interim data are comparable to data from recent atherosclerosis trials evaluating treatment methods such as statins.

The Phase IIb Canadian Antioxidant Restenosis Trial-2 (CART-2) was originally designed to evaluate AGI-1067 as a restenosis therapeutic, with atherosclerosis plaque volume as a secondary endpoint. However, after the company's CART-1 trial showed the compound's potential for reducing plaque, AGIX changed course and made this the primary objective of the study.

In August 2003, enrollment in CART-2 was capped after 467 patients had undergone elective angioplasty. Late last month, AGIX decided to take an early look at the data to help guide its decision on whether to commit to a substantial investment in scale-up manufacturing for AGI-1067. FDA approved the interim analysis, giving the trial a 0.001 penalty, changing the final requirement for statistical significance on the primary endpoint, change of plaque volume from baseline, from 0.05 to 0.049.

Plaque was measured using intravascular ultrasound (IVUS) during the angioplasty procedure and again after one year.

As a result of the course change, some of the patients already enrolled in the trial wouldn't have been enrolled in a coronary artery disease study, and thus all of the IVUS scans evaluated in the trial would not have been included. AGIX (Alpharetta, Ga.) had two labs read the scans in a blinded manner to identify those most suitable for analysis in an atherosclerosis study. The 133 patients included in the interim analysis were identified through this review.

As the company said it expected, only about 20% of the IVUS scans were evaluated as a part of the interim results. This was due to dropouts and inadequate scans that did not meet the prespecified criteria.

The interim analysis of combined data from the three AGI-1067 groups showed reduced plaque volume by an average of 6.4 mm^3 (3.8%) from baseline ($p<0.0003$) *(see "AGI-1067 by the Numbers," A16)*.

The company said the difference between the AGI-1067 groups and placebo was not significant because of the small number of patients in the interim analysis.

In the most severely diseased subsegment of each patient's arteries, a secondary endpoint, treatment also led to a significant ($p<0.0001$) regression from baseline by an average of 2.7 mm^3 (7.1%). In these subsegments, AGI-1067 did significantly reduced plaque volume versus placebo ($p<0.02$).

AGIX expects to be able to evaluate about 260 of the scans from all 467 patients and disclose the data before year end.

The CART-2 results stack up well against data from the REVERSAL statin study. That trial, in 502 evaluable patients, showed that 80 mg/day of Lipitor atorvastatin from Pfizer Inc. gave a median 0.4% reduction in total plaque volume from baseline after 18 month, which wasn't significant *(see "Tell-Tale Signs")*.

The results of CART-2 also are comparable to those seen in a Phase II trial of ETC-216 from Esperion Therapeutics Inc. In the 57-patient study, patients given five doses of ETC-216, a variant of apolipoprotein A-I HDL, had a mean atheroma volume decrease of -1.06% compared to baseline (p=0.02) versus an increase of 0.14% in the placebo group *(see BioCentury, Nov. 10, 2003)*.

Due in large part to those results, PFE (New York, N.Y.) acquired Esperion (Ann Arbor, Mich.) last December for about $1.3 billion in cash *(see BioCentury, Jan. 5)*.

See next page

Tell-tale signs

The results of the CART-2 study showed AGI-1067 from AtherogGenics (AGIX) significantly reduced plaque volume from baseline. The results reinforce similar data from CART-1. The CART-2 results also compare favorably to results from the REVERSAL study, which showed high dose statins inhibited atherosclerotic plaque progression compared to low-dose statins, as well as with the results of a Phase II trial of ETC-216 from Esperion (ESPR) that showed the variant of apolipoprotein A-I HDL reduced plaque volume. P values are for within group analyses; NS = not significant

	Chg in atheroma volume	P value
REVERSAL		
Lipitor atorvastatin	-0.4%	p=NS
Pravachol pravastatin	2.7%	p=0.001
Patients received either 80 mg/day Lipitor from Pfizer (PFE) or 40 mg/day Pravachol from Bristol-Myers Squibb (BMY) and underwent IVUS at baseline and 18 months.		
Esperion		
ETC-216	-1.06%	p=0.02
Placebo	0.14%	p=NS
Patients received five weekly infusions and underwent IVUS at baseline and within two weeks of the final dose.		
CART-1		
AGIX-1067 280 mg	-1.63%	p=0.04
AGIX-1067 140 mg	-1.88%	p=0.04
Placebo	0.50%	NA
Patients received AGI-1067 or placebo for six weeks and underwent IVUS at baseline and at six months.		
CART-2		
AGIX-1067 280 mg	-3.8%	p<0.003
Placebo	-2%	p=NS
Patients received AGI-1067 for varying periods and underwent IVUS at baseline and 12 months.		

CART changed its horse,
from previous page

In CART-2, patients were randomized into three treatment groups: one group received AGI-1067 for 14 days prior to surgery; one group received AGI-1067 for three days prior to surgery; one received placebo for 14 days prior to surgery. All three received AGI-1067 for 12 months following surgery. A fourth group received placebo before and after surgery.

The dose of AGI-1067 was 280 mg per day given orally. All groups received standard of care, including statins and other anti-atherosclerotic therapy.

AGIX also is running the Phase III ARISE trial in 4,000 patients with coronary artery disease. Unlike the CART trials that compared AGI-1067 to baseline, ARISE will evaluate clinical event measures such as death due to coronary disease, myocardial infarction, stroke, coronary re-vascularization and unstable angina.

Russell Medford, president and CEO, said that the company expects to include data from the trial in an NDA submission by the end of 2005.

AGI-1067 by the numbers

AtheroGenics (AGIX) had two labs — the Montreal Heart Institute (MHI) and Cleveland Clinic Foundation (CCF) — independently analyze interim data from the CART-2 trial. The analyses suggest that AGI-1067 significantly reduced the plaque volume in 133 patients, while inducing an even greater change in the most severely diseased subsegment of patients' arteries. P values are for within group analyses and are in comparison to baseline; NS = not significant

Reductions in plaque volume - primary endpoint				
	MHI	P value	CCF	P value
AGI-1067	5.4 mm3 (3.3%)	p<0.003	7.4 mm3 (4.2%)	p<0.0006
Placebo	2.6 mm3 (1.6%)	p=NS	4.4 mm3 (2.4%)	p=NS
Reductions in plaque volume - most diseased subsegment				
	MHI	P value	CCF	P value
AGI-1067	2.4 mm3 (6.3%)	p<0.0001	3.0 mm3 (8.0%)	p<0.0001
Placebo	1.4 mm3 (3.6%)	p=NS	1.3 mm3 (3.5%)	p=NS

Online links this week

Links to the following documents reside online at BioCentury's News Center at www.biocentury.com.

Disclosure

Updates to CDER's manual of policies and procedures involving the public dissemination of pharmacology reviews of pediatric studies, and for tertiary review of genetic toxicology studies resulting in a recommendation for a clinical hold or conduct of additional studies.

Electronic data

FDA draft guidance on the use of computerized systems for maintaining and retrieving clinical trial data.

Follow-on biologics

Presentations from Sept. 14-15 FDA workshop on scientific considerations related to developing follow-on protein products.

International Conference on Harmonization

FDA announcement of an Oct. 19 public meeting to discuss the ICH process and the Nov. 15-18 meeting of the ICH in Yokohama, Japan.

Manufacturing

— Final FDA report on its Pharmaceutical Current Good Manufacturing Practices for the 21st Century initiative.
— FDA draft guidance on good manufacturing practice for combination products.
— FDA white paper on the role of quality systems in pharmaceutical cGMP regulations.
— FDA guidance on process analytical technology (PAT) as a regulatory framework for development, manufacturing, and quality assurance.

Reimportation

Four drug reimportation bills proposed by the California legislature and vetoed by Gov. Arnold Schwarzenegger: SB 1144; SB 1149; SB 1133; and AB 1957 *(see A19).*

Product documentation

—Cancidas: Revised EPAR for Cancidas caspofungin to treat invasive aspergillosis in adult patients, from Merck & Co. Inc. (MRK).
—Palladone: FDA approval letter for Palladone hydromorphine to treat persistent, moderate to severe pain in patients requiring continuous opioid analgesia for an extended period, from Purdue Pharma L.P.
—Temocillin: COMP positive opinion for temocillin sodium to treat Burkholderia cepacia lung infection in cystic fibrosis patients, from Belpharma N.V.
—Vioxx: FDA public health advisory regarding the worldwide withdrawal of arthritis drug Vioxx rofecoxib due to safety concerns related to an increased risk of cardiovascular events, from Merck & Co. Inc. (MRK) *(see A13).*

Product Development

No pain AND no gain

By Kathryn Calkins
Senior Writer

People who need to lose weight want to do so without feeling like they are constantly hungry. Nastech Inc. says that its intranasal version of the natural hormone PYY 3-36 induces a feeling of satiety in patients that measurably reduces their calorie intake. Merck & Co. Inc. last week entered into a deal with NSTK to develop the compound, which would add to the pharma company's pipeline of obesity compounds in Phase I and Phase II development.

According to Steven Quay, NSTK's chairman, president and CEO, PYY 3-36's mechanism of action is different from most other compounds being tested in obesity. The native hormone, PYY, is produced by L cells in the gut in response to the number of calories a person consumes. From there, it is released into the bloodstream. "So, if you just eat a snack or if you gorge yourself, you'll get different levels of PYY produced," he said.

'If you just eat a snack or if you gorge yourself, you'll get different levels of PYY produced.'

— Nastech's Steven Quay

PYY 3-36 is the 33-amino acid portion of the hormone that is cleaved from its initial form by the body to become active.

PYY travels to the arcuate nucleus, a portion of the hypothalamus that has no blood-brain barrier because it must measure various components of blood. Once there, the hormone binds to the Y2 receptor, which is one of the five neuropeptide Y families. "Y1 induces feeding behavior, and Y2 does the opposite. It induces satiety," Quay said.

Programs looking directly at neuropeptide Y (NPY) for obesity have not met with much success. For example, Neurogen Corp. (NRGN, Branford, Conn.) and partner Pfizer Inc. (PFE, New York, N.Y.) worked from 1995 through 2000 on compounds inhibiting the Y1 and Y5 receptors that stimulate feeding behavior. According to NRGN spokesperson Tom Pitler, both PFE and NRGN found the NPY mechanism less potent than they had hoped, and the research was concluded.

By contrast, academic-sponsored trials in humans have shown that giving PYY 3-36 reduces a person's calorie intake during a meal. For example, in a double-blind, placebo-controlled study of 12 obese and 12 lean patients in the U.K., caloric intake during a buffet lunch provided two hours after an infusion of hormone fell by 30% in obese patients ($p<0.001$) and by 31% in lean patients ($p<0.001$) *(see BioCentury, Sept. 8, 2003).*

Quay noted that such a reduction in daily calories over one year would equate to a 50-pound weight loss. By comparison, in Phase III trials, Meridia sibutramine from Abbott Laboratories (ABT, Abbott Park, Ill.) produced an average weight loss over one year of 9.8 pounds at the 10 mg dose and 14 pounds at the 15 mg dose compared with 3.5 pounds in the placebo group. Meridia is a neurotransmitter reuptake inhibitor marketed to treat obesity.

As promising as PYY's effect appears, Quay noted that physicians would balk at having to administer the compound via a 90-minute infusion, as was done in academic trials. Thus, NSTK formulated PYY 3-36 with an excipient that temporarily relaxes the tight junctions between cells in the nasal mucosa to allow wicking of the formulation across the mucosa. "The two compounds are formulated together, but they are not chemically linked," he said.

In a placebo-controlled Phase Ic trial in 37 patients, those receiving PYY 3-36 reduced calorie intake by an average of 648 calories on the last day of the six-day study.

Reduction in caloric intake over all six days was related to the number of daily PYY administrations. Patients receiving one daily dose reduced their calories by a mean of 77; those receiving two doses reduced calories by a mean of 197; and those receiving three daily doses reduced calories by a mean of 490. Patients receiving three doses lost a mean of 1.3 pounds over six days *(see BioCentury, July 5).*

NSTK is not the only company thinking about how to deliver PYY 3-36. Amylin Pharmaceuticals Inc. (AMLN, San Diego, Calif.) has its AC162352, which is delivered subcutaneously, in Phase I trials. AMLN expects to complete the trial in the fourth quarter.

Atrix Laboratories Inc. (ATRX, Fort Collins, Colo.), has an Atrigel sustained-release formulation of PYY 3-36 in preclinical testing. QLT Inc. (TSE:QLT; QLTI, Vancouver, B.C.), which is acquiring ATRX, said it is too early to say whether it will continue the project.

Finally, Emisphere Technologies Inc. (EMIS, Tarrytown, N.Y.) has a preclinical project with an oral form of the hormone. Lewis Bender, senior vice president of business development, told BioCentury the company has delivered active hormone into the bloodstream of animals with its formulation.

He said that following NSTK's deal with MRK, EMIS is reevaluating its prioritization of the project.

MRK (Whitehouse Station, N.J.) paid $5 million up front for worldwide rights to NSTK's PYY formulation, which has completed three Phase I trials. NSTK is eligible for up to $341 million in milestones, plus royalties. It also has an option to co-promote the product in the U.S. and retains manufacturing rights.

Product Development

Bet on the placebo

The Phase II trial of Valentis Inc.'s Deltavasc gene therapy may have missed its endpoint in treating peripheral arterial disease (PAD), but the company thinks that all is not lost. The PINC polymer carrier portion of Deltavasc may be at least as efficacious as VLTS's angiogenic Del-1 gene and may provide an easier and cheaper route to market than the original gene therapy.

This week's briefing

VLTS's protective interactive non-condensing (PINC) polymer technology is intended to deliver genes into cells by integrating into the cell membrane, said Chairman, President and CEO Benjamin McGraw. It has hydrophobic and hydrophilic components designed to give it the characteristics of a membrane.

When the polymer alone was given to 51 control patients in the trial, it produced improvements similar to those seen in the treatment group on both the primary endpoint of exercise tolerance after 90 days and on ankle brachial index (ABI), a clinical indicator of blood flow. "Obviously, more is going on with PINC" than simply integration into the membrane, McGraw said.

The 49-patient treatment group received Deltavasc, which is PINC polymer plus Del-1, a gene with angiogenic properties. All groups received their injections intramuscularly.

Both arms improved significantly from baseline. At 90 days, the controls had an exercise tolerance improvement of 34% ($p<0.00001$), and the Deltavasc group had an improvement of 32% ($p<0.0001$). The control group's ABI improvement was 0.059 ($p=0.00072$), and the Deltavasc group's was 0.048 ($p=0.00665$).

There was a statistically significant correlation between improvements in peak walking time and ABI index in the study ($p=0.039$). This is important, McGraw said, because even when PAD trials in the past have produced high placebo effects on exercise tolerance measures, no effect on ABI has been seen.

When the company saw what was happening, it unblinded an ongoing study in rabbits comparing blood vessel formation in tissue following intramuscular saline injections, PINC injections and Deltavasc injections. To its surprise, both the PINC and Deltavasc groups had increased vessel density in tissue samples. The saline group did not.

VLTS (Burlingame, Calif.) will run additional preclinical studies to try to understand PINC's activity. McGraw said that the polymer is known to deplete ATP, which in turn upregulates adenosine, an angiogenic agent that increases blood flow.

Simultaneously, VLTS will go ahead with its PAD clinical program, switching from Deltavasc to PINC alone. It expects to have 180-day data from the Phase II trial this quarter, and plans to design a Phase III trial testing PINC as soon as possible.

According to McGraw, the switch to PINC will not affect VLTS's previously projected timeline for the program, which has initial Phase III trial data coming in the first half of 2006. However, it does simplify the program's regulatory path, moving the product from a biologic to a drug and eliminating the additional requirements for gene-based medicines.

The development process also will be cheaper, because VLTS will not have to scale up its gene production process. PINC production is already available at a scale to support pivotal trials.

VLTS, which had $20.5 million in cash at June 30, hopes to partner the compound sometime during Phase III. — *Kathryn Calkins*

Gentler sandman

Most insomnia drugs carry a warning that they may be habit forming and have undesirable CNS side effects. Most of these drugs work through GABA receptors that are widely distributed throughout the brain. But Takeda Pharmaceutical Co. Ltd. says its Ramelteon MT1 and MT2 melatonin receptor agonist is more targeted than GABA modulators because it more specifically affects the areas in the brain responsible for sleep. As a result, Takeda expects it will have fewer undesirable effects on learning, memory and motor activity.

Last week, Takeda (Osaka, Japan) submitted an NDA to FDA for Ramelteon to treat insomnia.

Melatonin MT1 and MT2 receptors are located mostly in the suprachiasmatic nuclei (SCN) found in the hypothalamus, according to Steven Sainati, vice president of clinical development.

Ramelteon's effects are mediated primarily through MT1 receptors, which are thought to regulate sleepiness. MT2 receptors are thought to modulate the circadian rhythm or the shift between sleep and wakefulness. "Basically Ramelteon tilts the balance in favor of the sleep mechanisms," he said. "Ramelteon initiates the processes which start the body's sleep cycle."

Neurons from the SCN have projections into other parts of the brain that are important for sleep. Sainati said these projections are relatively specific to the cortex.

Drugs that modulate GABA receptors also affect the SCN and slow down the same systems as Ramelteon, Sainati noted. "But by comparison, GABA receptors are widely distributed throughout the brain," he said. "GABA modulators can cause wooziness, ataxia and respiratory depression. Ramelteon acts via a mechanism that is independent and completely different than the GABA pathway."

Sainati declined to comment on the differences between Ramelteon and more selective GABA receptor modulators, which also have been shown to have fewer CNS side effects than older, more general GABA receptor modulators *(see BioCentury, Feb. 16)*.

Takeda also thinks Ramelteon is different from the naturally occurring melatonin hormone, Sainati said. "Ramelteon is very targeted, especially to MT1 receptors. Melatonin acts at all melatonin receptors and can have untoward affects. For example, certain cardiovascular side effects like coronary artery spasm have been observed with melatonin. We haven't seen anything like that in trials of Ramelteon."

A third type of melatonin receptor, MT3, is more widely distributed in the brain and also is found in peripheral tissue.

Takeda plans to market Ramelteon worldwide. — *Christopher Maggos*

Washington Notebook

Schwarzenegger's warning

By Steve Usdin
Washington Editor

California Gov. Arnold Schwarzenegger is trying to persuade pharmaceutical companies to offer deep discounts on drugs sold to uninsured, low-income state residents. If drug companies do not voluntarily provide price breaks acceptable to Schwarzenegger, he said last week that he will seek legislation to compel them to do so.

Schwarzenegger, a Republican, cited plans to establish a "California Rx" program as partial justification for vetoing four drug importation bills. The bills, all sponsored by Democrats, would have allowed the state to import drugs from Canada for Medicaid and an AIDS drug assistance program and required the state to post information on the Internet to help state residents import drugs from Canada.

This week's briefing

Schwarzenegger outlined his objections to the bills in memos to the state Senate. He noted that importing drugs from Canada violates federal law. He also wrote that importation proposals "over-simplify the complex safety, trade, supply and pricing issues involved in this marketplace."

Nevertheless, Schwarzenegger said that expanding access to affordable prescription drugs is a "top priority" of his administration. He revealed plans to introduce legislation in 2005 aimed at providing discounted drugs for uninsured Californians with incomes up to 300% of the federal poverty level. About 4.8 million people would be eligible, David Topp, assistant secretary of the California Health and Human Services Agency, told BioCentury.

According to Topp, Schwarzenegger started discussing California Rx with senior executives of drug companies a month ago, both in group meetings and in one-on-one telephone conversations. The governor has asked the companies to volunteer to sell drugs at prices below those provided to Medicaid, he said.

"We've designed the program so that we will fit into exemptions from Medicaid's 'best price' rules," so companies will not be obliged to extend the discounts to Medicaid, he said. "California will be more aggressive than any other states have been on negotiating discounts."

Topp declined to identify the companies that are negotiating with the state.

The discussions have emphasized outpatient prescription drugs, "but we are looking at injectables and hospital-administered drugs as well," he said.

According to Topp, the governor will negotiate with companies for another six weeks. The deadline was set to provide an opportunity to draft legislation in time for it to be introduced in January, he said.

Schwarzenegger said he prefers a voluntary program, but if that doesn't happen, he said he will work with the legislature to "develop an approach that guarantees significant reductions in prescription drug prices for California's low-income uninsured residents."

PhRMA's FOB thinking

The Pharmaceutical Research and Manufacturers of America has outlined a process for FDA to craft an abbreviated pathway for the approval of follow-on biologics. They just haven't told anybody.

PhRMA's board of directors approved a position statement on Sept. 15 that proposes a legislative and regulatory framework for FOBs. PhRMA has not released the document, which was generated for internal use, according to Jeff Trewhitt, a spokesperson for the trade association.

The position paper, which BioCentury has seen, charts a proposed path for the development of laws allowing FOBs. The statement says that following a transparent information-gathering process, FDA should write a concept paper addressing the scientific and intellectual property issues surrounding FOBs. This concept paper could be the basis for further discussion and ultimately for legislation.

The document also suggests PhRMA believes the give-and-take over FOBs is likely to end up with a compromise giving innovators a fixed term of data protection.

PhRMA's board stated that any legal and regulatory changes to allow an abbreviated application and approval process for FOBs should "incorporate strong intellectual property protections to promote innovation, including an assurance of a reasonable period of time during which safety and effectiveness data supporting an innovative approval could not be used for approval of a follow-on biologic developed by an unrelated manufacturer."

While the statement thus does not reject the concept of FOBs**,** PhRMA also notes the linkage between the manufacturing process and clinical attributes of biologic products and argues that "all follow-on biologic applications should be supported by appropriate studies using the investigational follow-on product."

It also asserts that it may be possible to approve follow-ons "based on scientifically justified different data sets from original innovative approvals." According to the document, "each follow-on product should be supported by data generated from appropriate preclinical work, clinical safety and effectiveness trials and robust postmarket surveillance, and a full chemistry, manufacturing, and controls section."

PhRMA's statement also tries to draw a fine line around section 505(b)(2) of the Food, Drug, and Cosmetic Act in an attempt to prevent its FOB position from having unintended consequences. While the trade group opposes use of the section to approve biologics that are regulated as drugs, such as human growth hormone and insulin, it wants to maintain the ability to use the section for approval of small molecules.

FDA has stated that section 505(b)(2) could be used to

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approve follow-on versions of biologics that are regulated as drugs, but it recently deferred action on Novartis AG's attempt to use the provision to obtain approval for Omnitrop, a generic hGH. Novartis (NVS; SWX:NOVN, Basel, Switzerland) is a PhRMA member.

PhRMA's internal debate can be discerned via the various drafts that the position paper went through. An Aug. 6 draft asserted that 505(b)(2) "is properly limited to 'paper NDAs' based on published studies," and should not allow a follow-on competitor to rely on the safety and efficacy of an approved drug, as is the case for generic applications under an ANDA. A paper NDA is an application supported entirely by preclinical data and published studies, with no new clinical data.

On Sept. 2, Wyeth Chairman, President and CEO Robert Essner wrote a letter to Amgen Inc. Chairman and CEO Kevin Sharer suggesting that the references to 505(b)(2) be modified to endorse use of the provision for actions that could be approved in a supplement to an ANDA, "such as a new dosage form, new route of administration, or Rx-OTC switch." AMGN (Thousand Oaks, Calif.) is chairing PhRMA's Follow-on Biologics Key Issues Team.

Essner's interest in the issue is not academic. WYE (Madison, N.J.) recently used 505(b)(2) to launch Allavert, a generic OTC version of Claritan antihistamine from Schering-Plough Corp. (SGP, Kenilworth, N.J.).

In order to prevent the statement from providing legal fodder for a challenge to the Allavert approval, the final version of PhRMA's statement includes a footnote qualifying its contention that 505(b)(2) should be limited to paper NDAs. The footnote is crafted to rule out references to the safety and efficacy of a pioneer product if it is a biologic, but to allow such references for drugs under the circumstances described in Essner's letter.

FDA will discuss the scientific issues associated with FOBs at a Drug Industry Association workshop in February. The agency then plans to issue a draft guidance *(see BioCentury, May 3 & Sept. 6).*

Congress is likely to begin consideration of FOBs in 2005, with the goal of enacting legislation in 2006, according to Capitol Hill staff.

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Ebb & Flow

The brave Atlantic alliance

By Shaun Brown & Steve Edelson Senior Writers

While European investors continue to put their money into the U.S., a change in the Paris Stock Exchange rules is making it easier for U.S. investors to hunt for bargains in Europe.

NicOx (NM:Nicox) last week became the first company to take advantage of the rule change, raising €26 million ($31.8 million) through a PIPE of 9.4 million shares at €2.75, a 15% discount to the closing price of €3.23 on Wednesday, the day prior to the announcement.

In June, the French government modified the so-called "Ordonnance" for French public companies looking to raise funds. The government dropped a regulation under which companies looking to raise cash from new investors had to use the average price for 10 days out of 20 to price an offering. The change makes it easier for public companies to offer investors a discounted price, as they do in U.S. PIPEs, rather than having to price an offer close to the market.

Under the new regulations, up to 15 new funds could invest in the offering. Of the funds that invested, 14 were U.S.-based, and one was from the U.K. The offer represents about 29% of the company's issued share capital and gives Nicox about €53 million ($64.9 million) in cash, enough to last three years.

"Continental European investors are not as experienced as U.S and U.K. investors, and under the new regulations we were only able to approach specialist funds," said CEO Michele Garufi. "In Europe, investors and analysts had basically written us off after the AstraZeneca deal fell through."

Last year, **AstraZeneca** (LSE:AZN; AZN) said that AZD3582 (HCT 3012), a nitric oxide (NO)-releasing naproxen, had not met the clinical endpoint in Phase II trials in osteoarthritis (OA) of the knee. Nicox reacquired rights to HCT 3012 and related COX-inhibiting NO-donator (CINOD) anti-inflammatory and analgesic compounds *(see BioCentury, Sept. 29, 2003).*

"This financing proves beyond doubt that Atlantic investors understand the potential of HCT 3012," said Garufi. "The cash allows us to accelerate development of the compound through Phase III studies and strengthens our position in negotiations with potential pharma partners for all our compounds."

Nicox now expects to begin a Phase III trial of HCT 3012 in the second half of 2005. Nicox also plans to start Phase III trials of NCX 4016, an NO-donating derivative of acetylsalicylic acid, in peripheral vascular disease (PVD) in 2006. The compound is currently in European Phase IIb studies.

Nicox closed the week up €0.22 to €3.47 with a market cap of €79 million ($97 million).

Money Raised in 2004

Total last week:	$508.9M
IPOs YTD:	$2228.2M
Follow-on YTD:	$2284.6M
Venture YTD:	$4097.3M
Other YTD:	$6470.2M
Total YTD:	$15080.4M

In 2003 a total of $19.7 billion was raised, including $509 million in IPOs, $3.8 billion in follow-ons, $4 billion in venture capital, and $11.3 billion in other fundraising. Totals include overallotments and warrants. *(Source: BioCentury Financial Center)*

More U.S. money for Europe

Bavarian Nordic (CSE:BAVA) and **Acambis** (LSE:ACM; ACAM) each won three-year NIH contracts to develop and manufacture 500,000 doses of third-generation Modified Virus Ankara (MVA) vaccines to prevent smallpox. Each contract includes an option for the U.S. government to purchase an additional 2.5 million doses *(see B2).*

The contracts are the second of three planned Requests for Proposals (RFP-II) in NIAID's smallpox vaccine tender program.

The BAVA contract is worth up to $141 million — $100 million for the first 500,000 doses of Imvamune (MVA-BN), and a potential $41 million for 2.5 million more. Imvamune is in Phase II studies for smallpox.

The ACM contract is worth up to $131 million, of which $76 million is for the first 500,000 doses, and $55 million is for the next 2.5 million. ACM's MVA vaccine, which is partnered with **Baxter** (BAX), is in Phase I.

The difference in contract size may be because BAVA's Imvamune is clinically more advanced. "We both have to do the same amount of work; however, the contract asks for further clinical development," said BAVA CSO Paul Chaplin. "Our further clinical development is in large Phase II studies, which will begin next year."

ACM also will have to run Phase II trials under the RFP-II contract.

On the week, BAVA was up DKK4 to DKK540 with a market cap of DKK2.5 billion ($410 million). ACM was up 5.8p to 302.3p with a market cap of £329 million ($594 million). On NASDAQ, ACAM was up $0.18 to $10.70.

CART racing

When **AtheroGenics** (AGIX) announced data from its first Phase II trial (CART-1) of atherosclerosis compound AGI-1067 in May 2001, investors exited the stock because the company said it couldn't determine whether the primary endpoint was met. The compound appeared to act faster than AGIX expected, confounding measurements. By October 2001, when AGIX and **Schering-Plough** (SGP) mutually ended their licensing deal for AGI-1067, the stock was trading at $2.71.

But it looks like both investors and SGP may have put the cart before the horse, as AGIX is up by an order of magnitude since then *(see "AtheroGenics Chronicles," A22).*

On Tuesday, the shares soared $14.84 (64%) to $38 on 28 million shares following Monday's post-market news that AGI-1067 met the primary endpoint of significantly reduced plaque volume from baseline in a preliminary analysis of a Phase IIb trial (CART-2) *(see "How CART Changed its Horse," A15).*

Pharmion's cornering speed

Pharmion (PHRM) might be able to turn the corner in 2005 — a year earlier than expected — thanks to strong sales of Vidaza, which is marketed to treat myelodysplastic syndromes. The company last week raised its second half sales guidance for Vidaza to $40-$45 million from $20-$27 million. Consequently,

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the company raised its full year net sales estimate to $111-$119 million from $91-$101 million.

PHRM has not said when it expects to become profitable, but the Street now expects 2005 EPS of $0.28. Prior to the announcement, the consensus estimate for next year was a loss of $0.05. This year, PHRM expects to post a loss of $0.90-$1.10 versus previous guidance of $1.40-$1.60. Still, PHRM was off $2.56 to $52.27.

IPO watch

San Diego-based **MediciNova** is taking its IPO plans across the Pacific and hopes to become another big money raiser on the Tokyo Stock Exchange's market of the high-growth and emerging stocks (MOTHERS). The specialty pharma play hopes to raise up to $100 million through Daiwa Securities.

MediciNova is no stranger to Japan. It was formed in 2000 as a majority-owned subsidiary of **Tanabe**, which now owns 14.9%. And MediciNova has tapped into the Japanese financial market before. In its $44 million series C round last month, about 70% of the funds came from Japanese investors.

MediciNova has one Phase I compound: MN-029, a second-generation tumor vascular targeting agent to treat solid tumors. By mid-2005, the company hopes to put three other compounds into Phase II testing: MN-221, an adrenergic beta 2 receptor agonist for premature labor; MN-001, an oral anti-inflammatory compound for interstitial cystitis and asthma; and MN-305, a serotonin (5-HT1A) receptor agonist for anxiety.

In general, MediciNova's strategy is to retain U.S. marketing rights to urology and gynecology indications and out-license the broader indications of asthma and anxiety.

In the first half of the year, MediciNova's operating loss was $26.7 million. The company had $15.2 million in cash as of June 30, which was before the C round closed. In addition to Tanabe, other principal stockholders in the company include Essex Woodlands (17.4% before the IPO); JAFCO (10.4%); Aqua RIMCO (8.7%); and Daiwa Securities (5.5%).

In July, **Sosei** (Tokyo:4565) raised $104 million on MOTHERS *(see BioCentury, July 26).*

In the U.S., **CardioVascular BioTherapeutics** filed to raise $20 million in an IPO through the sale of 2 million shares at $10. The company has a single product: its Cardio Vascu-Grow is in Phase I/II testing to treat cardiovascular disease. The compound is an undisclosed protein that promotes the growth of blood vessels in the heart.

In the first half of the year, the company had an operating loss of $1.6 million. CardioVascular had $6.4 million in cash as of June 30.

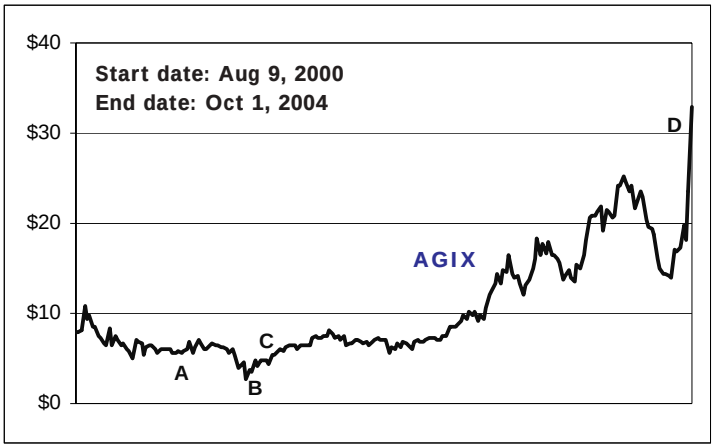
First Dunbar Securities is underwriting the deal. Prior to the IPO, company directors and officers own 91%.

Dutch treat

Merchant bank Dutchess Private Equity ventured into biotech last week, setting up a financing facility with penny stock **DNAPrint genomics**. Portfolio manager Doug Leighton told Ebb & Flow that the pharmacogenetics company "is probably the least expensive stock we've ever been in. Our general market cap band is $50-$100 million." Based on Friday's close of $0.018, DNAP is valued at $12 million.

AtheroGenics chronicles

Selected events tracked against AtheroGenics' weekly price since the company's August 2000 IPO.



A. 5/21/01 - AGIX said it could not determine whether AGI-1076 met the primary endpoint in a Phase II trial (CART-1) to treat restenosis following angioplasty

B. 10/4/01 - AGIX regains rights to AGI-1067 from Schering-Plough (SGP)

C. 11/12/01 - Final CART-1 data show the compound did meet the primary endpoint

D. 9/28/04 - Interim data from CART-2, a Phase IIb trial, show that AGI-1067 met the primary endpoint of a significant reduction in atherosclerosis plaque volume from baseline

Under the facility, DNAP can put up to $35 million of stock to Dutchess over the next two years.

As it turns out, a lot of Dutchess' money will make its way overseas: In conjunction with the financing facility, DNAP announced plans to take a majority stake in Germany's **Biofrontera**. DNAP plans to invest $25 million in Biofrontera over two years, which would give it a 51.8% stake. The goal, said DNAP, is to use its pharmacogenetics capabilities to stage patients for trials of Biofrontera's BF-Derm1, which is in Phase II testing to treat chronic itching and scratching.

Leighton noted that Dutchess did not invest in DNAP in order to get a piece of Biofrontera. "We'd been talking to DNAP since January and were interested in them first. Biofrontera came along and liked our structure."

Private rounds

Cellective raised $27.5 million in a series A round. The company, which is developing antibodies for cancer and autoimmune disorders, also named Arthur Mandell as president and CEO. Mandell previously was president and CEO of Stemron. Before that, he was senior vice president and chief business officer at **Human Genome Sciences** (HGSI). Investors in the round were Intersouth; Alta Partners; BA Venture Partners; Forward Ventures; **Genentech** (DNA); Latterell; MedImmune Ventures; and Sofinnova.

Coley raised $25 million in a series G round with Thomas McNerney; Venrock; TVM Techno Venture Management; and Global Life Science Ventures. The company plans to use the funds

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to develop its CpG-containing oligonucleotides for cancer and infectious diseases. Coley's ProMune is in Phase II trials for non-small cell lung cancer and melanoma. Next year, the company hopes to start Phase II testing of its Actilon to treat HCV.

VC tracks

Advanced Technology Ventures hired Richard Popp as a technology partner on the firm's healthcare team. He'll remain professor of medicine in the division of cardiovascular diseases at Stanford University's School of Medicine. ATV has more than $1.5 billion under management.

Regulatory milestones

OSI (OSIP) slipped $0.26 to $63.45 on the week, while partner **Genentech** (DNA) gained $1.33 to $53.16 after FDA accepted for filing their NDA for Tarceva as monotherapy to treat advanced non-small cell lung cancer. The PDUFA date is Jan. 30. The small molecule EGF receptor inhibitor also is partnered with **Roche** (SWX:ROCZ). The FDA action and ROCZ's MAA submission in August triggered a $10 million milestone payment to OSIP from the two partners.

Chiron (CHIR) was up $0.54 to $44.78 on the week, and **Gen-Probe** (GPRO) was off $0.10 to $40.49 after the partners submitted a BLA to FDA for their Procleix Ultrio blood screening assay to detect HIV-1, HCV and HBV. The companies already have an approved HIV-1/HCV assay.

Inex (TSE:IEX) popped C$0.95 (23%) to C$5.15 on the week, and partner **Enzon** (ENZN) gained $0.98 to $16.25 on news that FDA's Oncologic Drugs Advisory Committee will review their NDA for Marqibo on Dec. 1. The liposomal formulation of vincristine is under review to treat relapsed, aggressive non-Hodgkin's lymphoma (NHL) and has a Jan. 15 PDUFA date.

Ilex (ILXO) also will be at the Dec. 1 meeting, where ODAC will review the NDA for clofarabine to treat refractory or relapsed acute leukemia in children. ILXO has U.S. and Canadian rights to the purine nucleoside analog under a license from **Bioenvision** (BIVN). The PDUFA date is Dec. 30. **Genzyme** (GENZ), which is acquiring ILXO, was off $0.93 to $55.46 on the week. BIVN advanced $0.56 to $8.06.

Biogen Idec (BIIB) moved up $3.20 to $62.87 on the week, and **Elan** (ELN) was unchanged at $23.35 after the companies submitted an MAA for their Antegren natalizumab to treat Crohn's disease. The antibody is under review for multiple sclerosis (MS) in the EU, Canada and the U.S.

MGI Pharma (MOGN) was down $1.78 to $26.89 on the week, and **SuperGen** (SUPG) was up $0.12 to $6.05 after they submitted an MAA for Dacogen to treat myelodysplastic syndromes. MOGN received exclusive worldwide rights from SUPG to the compound in September. The companies hope to complete a rolling NDA submission by year end.

Millennium (MLNM) was up $0.02 to $13.40 on the week after submitting an sBLA for an expanded label for multiple myeloma drug Velcade. The company is seeking approval of the proteasome inhibitor in patients who have had at least one prior therapy. The drug, approved in the U.S. and EU for use in patients who have received two prior therapies, is partnered with **Johnson & Johnson** (JNJ).

Miravant (MRVT) fell $0.19 (11%) to $1.56 on Thursday but ended the week up $0.05 at $1.67 after an FDA approvable letter asked for another trial of the company's SnET2 photodynamic therapy to treat wet age-related macular degeneration. In 2002, two Phase III trials missed the primary endpoint of visual stabilization in the intent to treat population. However, the endpoint was met in the per protocol patient population — those receiving the minimal exposure to the treatment regimen specified in the clinical protocol. The company took its lumps the previous week, when it fell 32%.

Allergan (AGN) did not recover from its Monday losses and closed the week down $4.45 at $73.44 after receiving a not approvable letter for its oral tazarotene to treat moderate to severe psoriasis. In July, an FDA panel voted against recommending approval. AGN, which fell $2.25 to $75.64 last Monday when it announced the letter, markets a topical formulation of the compound to treat psoriasis and acne.

Clinical milestones

Valentis (VLTS) plunged $4.29 (65%) to $2.36 on 9.7 million shares on Wednesday after its Deltavasc plus PINC polymer missed the primary endpoint in a Phase II study in patients with peripheral arterial disease (PAD). The combination didn't show significant improvements in exercise tolerance compared the polymer alone. Going forward, VLTS plans to run a Phase III study of just the polymer *(see "Bet on the Placebo," A18).* VLTS closed Friday at $2.43, down $3.56 (59%) on the week.

Nabi (NABI) popped $1.79 (15%) to $13.48 on 4.6 million shares on Tuesday and closed the week up $2.32 (20%) at $14.09 after its NicVAX nicotine conjugate vaccine improved the quit rate in a Phase II trial for smoking cessation. NABI hopes to report full data from the trial next year *(see B12).*

Oscient (OSCI) was down $0.20 to $3.55 after its Factive gemifloxacin met the primary endpoints in two Phase III trials in acute bacterial rhinosinusitis *(see B13).* The antibiotic already is marketed to treat acute exacerbations of chronic bronchitis (AECB) and mild to moderate community-acquired pneumonia (CAP), and OSCI said it would increase the size of its Factive sales force to about 250 from 100.

NitroMed (NTMD) wasn't hit too hard on news that it and **Merck** (MRK) placed on hold a Phase II trial of a nitric oxide(NO)-enhancing version of rofecoxib. The news came on Thursday, after MRK announced that it was pulling Vioxx rofecoxib from all markets

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Restructuring watch

Just one public biotech company cut heads in September, down from six companies in the same month last year. So far this year, 26 companies have restructured compared to 65 in 2003. (A) Full year loss extrapolated from the first half loss of SEK59.7 million ($7.9 million), SEK=$0.13; $M

Date	Company	Staff cuts	Cash	Years cash pre-cut	Cash reporting date	Oper loss
9/13	**Karo Bio** (SSE:KARO) (A)	21% to 75	$16.6	1.1	6/30	$7.9

Cuts mainly in early drug discovery. Refocusing to advance selected projects into clinical trials.

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worldwide. The companies have other NO COX-2 inhibitors in development, and the deal remains intact. NTMD slipped $0.66 to $23.84 on Thursday and ended the week down $1.50 at $23.25.

Onyx (ONXX) was down $0.59 to $42.57 on the week after its BAY 43-9006 gave seven partial responses, five minor responses and 59 cases of stable disease in a Phase II trial in 137 advanced hepatocellular carcinoma patients *(see B12).* The small molecule, partnered with **Bayer** (FSE:BAYG; BAY), is in Phase III testing for renal cell carcinoma.

Enzo (ENZ) was up $0.22 to $15.30 on the week after its Alequel met the endpoints of clinical response and clinical remission in a Phase II study in patients with Crohn's disease *(see B11)*. ENZ said it is expanding the trial.

Angiotech (TSE:ANP; ANPI) was up C$1.60 to C$25.47 on the week after **Boston Scientific** (BSX) reported that the one-year benefits seen with BSX's Taxus paclitaxel stent were maintained after two years *(see B9).* BSX has rights from ANP to use paclitaxel in stents. On NASDAQ, ANPI gained $1.45 to $20.10 on the week.

Medarex (MEDX) closed Friday at $7.67, up $0.17 on the week after starting a Phase III trial of its MDX-010 antibody to treat metastatic melanoma *(see B14).*

Connetics (CNCT) gained $1.86 to $26.91 on the week after starting a Phase III trial of its Desilux to treat atopic dermatitis in infants and adolescents *(see B14).* The company hopes to submit an NDA for the topical steroid by the end of 2005.

Ebb & Flow

Nastech (NSTK) added to its gains from last Monday, when it surged $5.41 (70%) to $13.15 on 14.4 million shares after partnering its PYY 3-36 obesity compound with **Merck** (MRK). NSTK will receive $5 million up front and is eligible for $131 million in development and regulatory milestones, plus $210 million in sales-related milestones, plus royalties *(see "No Pain AND No Gain," A17).* NSTK closed Friday at $13.11, up $5.37 (69%) on the week.

Helping the stock along were multiple media reports that Merck's withdrawal of Vioxx from the market will make the pharma company more reliant on pipeline compounds. Some of the articles highlighted MRK's newly added obesity compound from the NSTK deal.

London & the Continent

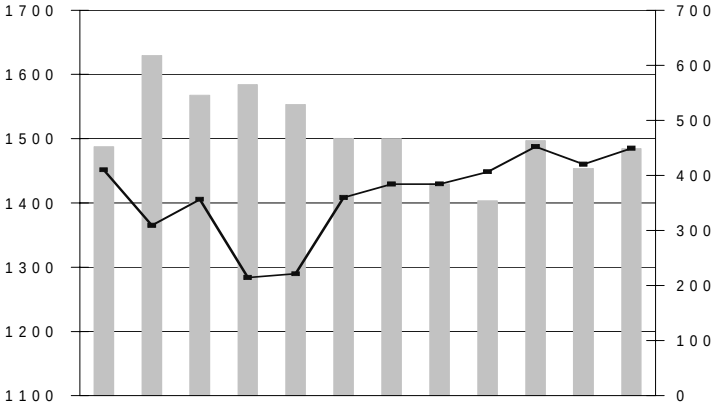
Cambridge Antibody Technology (LSE:CAT; CATG) was up 96.5p (19%) to 613p on the week on speculation that CAT will either settle its Humira adalimumab royalty dispute with **Abbott** (ABT) prior to the November court date or win outright in the London court. On Friday, Lehman analyst Sam Williams said he estimates 20% upside potential for a settlement and 43% upside potential for a court victory *(see "Analyst Picks & Changes").* CAT has a market cap of £224 million ($405 million). On NASDAQ, CATG was up $1.41 (15%) to $10.82.

Analyst picks & changes

Company	Bank	Analyst	Coverage	Opinion
AtheroGenics (AGIX)	Lazard	Joel Sendek	Price target	Buy
	Needham	Mark Monane	New	Underperform
Sendek raised his target to $71 from $27 to reflect the value of AGI-1067. Based on positive interim results from the Phase IIb CART-2 trial, he expects positive data from the Phase III ARISE trial and a partnership deal with a 20-25% royalty rate *(see A15).*				
Monane believes the market overreacted to data from AGIX's Phase IIb CART-2 trial of AGI-1067, which included 133 patients out of an expected 500. He said the risk/reward profile at this stock price is unattractive. AGIX closed Friday at $32.93, up $9.34 (40%) on the week.				
Cambridge Antibody (LSE:CAT; CATG)	Lehman	Sam Williams	Price target	Overweight
Williams raised his target to 820p from 650p. He believes CAT will either settle the dispute with **Abbott** (ABT) regarding royalties on Humira adalimumab, or win outright in court. CAT closed Friday at 613p, up 96.5p (19%) on the week.				
MGI Pharma (MOGN)	JMP Securities	Charles Duncan	Other	Market outperform
Duncan lowered his FY04 EPS estimate to $0.06 from $0.23 to reflect a $12.5M milestone payment owed to **SuperGen** (SUPG) under last month's development and marketing deal for SUPG's Dacogen decitabine to treat myelodysplastic syndromes (MDS). MOGN closed Friday at $26.89, down $1.78 on the week.				
New River (NRPH)	Wells Fargo	Robert Uhl	New	Buy
Uhl set a $19 target. NRPH closed Friday at $10.33, up $1.28 (14%) on the week.				
Pharmion (PHRM)	Pacific Growth	Gregory Wade	Other	Overweight
Wade raised his FY04 revenue estimate for Vidaza azacitidine to $43.6M from $38.1M after management raised its guidance to $40-$45M from $20-$27M. Vidaza was launched in the U.S. on July 1 to treat myelodysplastic syndromes (MDS). PHRM closed Friday at $52.27, down $2.56 on the week.				
VaxGen (VXGN)	Punk	Sharon Seiler	Price target	Buy
Seiler raised her price target to $15 from $11 after VXGN resolved issues associated with warrants issued in 2001. Seiler said the new agreement eliminates monthly penalty payments of $150,000-$600,000 and additional cash outlays of at least $3.9M. VXGN closed Friday at $13.41, up $0.65 on the week.				
Vertex (VRTX)	SunTrust	David Witzke	New	Neutral
Witzke said a lack of near-term clinical catalysts could make it difficult for VRTX to outperform the market in the next 12 months. VRTX closed Friday at $10.59, up $0.75 on the week.				

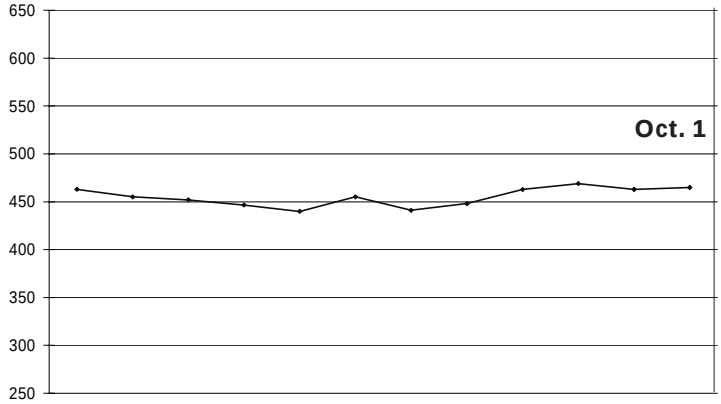
BioCentury 100 Price & Volume Trend

Cumulative weekly performance of 100 bioscience stocks. 12-week period. Line shows Price Level change (Left scale. Index base=1000 on May 10, 1996). Bars show cumulative volume in millions (right scale).



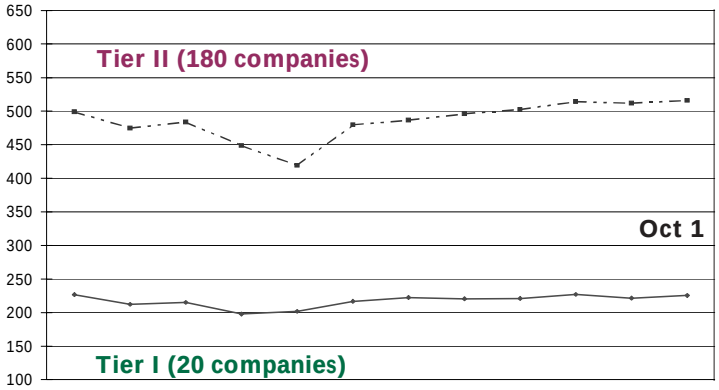
BioCentury London Index

Weekly change in the combined market capitalization for 14 bioscience stocks listed on the LSE or AIM, 12-week period. Index base =1000 on May 10, 1996.



TFCG Life Sciences Indexes

Weekly change in combined market capitalization. 12-week period. Tier I = market caps>$1B; Tier II <$1B. Base =100 on Dec. 31, 1998.



Source: Thomson Financial

BioCentury tracks 486 issues that report prices and volume daily. The BioCentury 100 is a subset used to monitor price and volume trends. TFCG Life Sciences Indexes are compiled by Thomson Financial, provider of market intelligence services to publicly held companies.

Price Gains

Stocks with greatest % price increase in the week ended Oct. 1. (Priced above $2.50; 25,000 minimum share volume)

Company	Ticker	$Close	$Chg	%Chg	Vol(00)
Nastech	NSTK	13.110	5.370	69%	339101
AtheroGenics	AGIX	32.930	9.340	40%	459114
Lynx	LYNX	2.600	0.730	39%	11754
Resverlogix	RVX	C3.500	C0.850	32%	2006
Ciphergen	CIPH	4.190	0.920	28%	15582
Access	AKC	5.660	1.110	24%	3860
Third Wave	TWTI	7.460	1.420	24%	29560
Myogen	MYOG	8.020	1.520	23%	5357
Inex	IEX	C5.150	C0.950	23%	3080
Nabi	NABI	14.090	2.320	20%	70342
Progenics	PGNX	14.630	2.200	18%	3670
Northfield	NFLD	14.300	1.960	16%	6696
Cambridge Antib[1]	CATG	10.820	1.410	15%	25026

Price Declines

Stocks with greatest % price decline (criteria as above).

Company	Ticker	$Close	$Chg	%Chg	Vol(00)
Exact	EXAS	3.200	-0.610	-16%	12524
Mannkind	MNKD	19.620	-3.630	-16%	32533
Human Genome	HGSI	10.930	-1.740	-14%	175036
Martek	MATK	47.620	-6.700	-12%	57873
Vical	VICL	4.550	-0.570	-11%	3854
Pharmos	PARS	2.730	-0.340	-11%	50039
Sangamo	SGMO	4.860	-0.580	-11%	1246
Momenta	MNTA	7.800	-0.890	-10%	5440
Phase Forward	PFWD	8.070	-0.880	-10%	9588
Kosan	KOSN	5.880	-0.630	-10%	8049
Emisphere	EMIS	2.910	-0.300	-9%	6874
Immtech	IMM	9.430	-0.970	-9%	3704

Volume Gains

Greatest changes in volume above 25,000 shares.

Company	Ticker	Vol(00)	%Chg	$Close	$Chg
Nastech	NSTK	339101	6670%	13.110	5.370
OxiGene[2]	OXGN	97378	1725%	5.980	0.420
Acadia	ACAD	3024	964%	7.800	0.800
Acusphere	ACUS	3575	761%	6.220	-0.230
Point Therapeutics	POTP	2622	626%	4.380	0.470
Corautus	CAQ	2795	613%	5.340	0.070
bioMerieux	BIM	3312	541%	€28.25	€0.800
Santarus	SNTS	24614	539%	9.330	-0.420
NeuTec	NTP	2072	523%	472.5p	5p
Aclara	ACLA	6484	426%	3.960	0.31
AtheroGenics	AGIX	459114	420%	32.930	9.340

1 Includes volume from London Stock Exchange with converted ADSs (ADS = 1 share)
2 Includes colume from Stockholm Stock Exchange

BioCentury 100 Advance-Decline Trend

Week ended	BC100 Price level	BC100 Stocks gaining	Gaining vol. (00)	BC100 Stocks declining	Declining vol. (00)
Sep 03	1429.64	45	1639376	52	2045960
Sep 10	1448.53	73	2201359	27	1337266
Sep 17	1487.71	73	3596648	26	1019361
Sep 24	1460.35	25	1228403	73	2885484
Oct 01	1485.31	68	2922401	30	1367500

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10TH ANNUAL INTERNATIONAL PARTNERING CONFERENCE

BIO-EUROPE 2004

10TH INTERNATIONAL PARTNERING CONFERENCE

Building Value through Partnerships

November 8–10, 2004
Congress Center West
Cologne, Germany

A forum to promote business among the pharmaceutical, biotechnology and financial industries.

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Bio
BIOTECHNOLOGY INDUSTRY ORGANIZATION

E.B.D. GROUP
International Business Development For The Life Sciences

EMERGING BIOPHARMACEUTICAL ENTERPRISES

BioCentury Part II

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Using BioCentury Part II

BioCentury Part II is a comprehensive compendium of business news for management and investors in bioscience companies. It is organized into three departments: Company News, Clinical News and Financial News.

The index on this page lists all the companies covered this week. The news items in each department are organized alphabetically by company. When more than one company is listed, the biotech company is shown first. Each brief is labeled with one or more applicable business categories from the following list:

ADMET; Agbio/Environmental; Antibodies; Autoimmune; Bioinformatics; Biomanufacturing; Biopharmaceuticals; Cancer; Cardiovascular; Chemistry; Combinatorial biology; Computational chemistry/biology; Dental; Dermatology; Diagnostic; Drug delivery; Endocrine; Finance; Functional genomics; Gastrointestinal; Gene/Cell therapy; Generics; Genitourinary; Genomics; Hematology; Hepatic; High throughput screening; Infectious; Inflammation; Metabolic; Microarrays; Microfluidics; Musculoskeletal; Neurology; Nutraceuticals; Ophthalmic; Other; Pharmaceuticals; Pharmacogenetics; Proteomics; Pulmonary; Renal; Supply/Service; Transplant; Veterinary

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COMPANY NEWS/Deals, Sales & Marketing, Management Tracks

DEALS

Acambis plc (LSE:ACM; ACAM), Cambridge, U.K.
Bavarian Nordic A/S (CSE:BAVA), Copenhagen, Denmark
National Institutes of Health, Bethesda, Md.
Business: Infectious diseases

The NIH's National Institute of Allergy and Infectious Disease awarded smallpox Modified Vaccinia Ankara (MVA) vaccine contracts to both ACM and BAVA. The three-year contracts are the second of three planned Requests for Proposals (RFP-II) in NIAID's smallpox vaccine tender program. Both companies were awarded contracts under RFP-I.

BAVA's new contract is worth up to $141 million. BAVA will receive $100 million to manufacture 500,000 doses of Imvamune (MVA-BN). The U.S. government has an option to purchase an additional 2.5 million doses for $41 million. Imvamune is in Phase II studies for smallpox. The contract requires further clinical development of Imvamune and validation of animal models.

The new ACM contract is worth up to $131 million. ACM will receive about $76 million for further development and manufacture of 500,000 doses of its MVA vaccine. ACM may receive another $55 million if the government exercises its option to purchase an additional 2.5 million doses. ACM's MVA vaccine, which is partnered with Baxter Healthcare Corp. (BAX, Deerfield, Ill.), is in Phase I trials.

Accelrys Inc. (ACCL), San Diego, Calif.
SciTegic Inc., San Diego, Calif.
Business: Bioinformatics

ACCL completed its previously announced acquisition of SciTegic for $12.25 million in cash and about 1 million ACCL shares *(see BioCentury, Sept. 20)*. Using ACCL's close of $5.76 on Sept. 28, the deal is valued at $18.5 million.

Agrisoma Biosciences Inc., Burnaby, B.C.
Dow AgroSciences LLC, Indianapolis, Ind.
Business: Veterinary

The companies partnered to research, develop and commercialize animal health products. The deal combines Agrisoma's ACE System for delivering and expressing genes in plants with Dow's plant systems. Agrisoma will receive upfront payments and research funding and is eligible for milestones and royalties.

Akzo Nobel NV (Euronext:AKZ; AKZOY), Arnhem, the Netherlands
Hemosol Corp. (TSE:HML; HMSL), Toronto, Ontario
Business: Hematology

HML will exclusively manufacture Hepalean heparin sodium from Organon Ltd. (Scarborough, Ontario) for sales in Canada for an initial three years. Organon is a subsidiary of AKZ. Hepalean will be launched in early 2005 to treat thrombophlebitis, phlebothrombosis, and cerebral, coronary and retinal vessel thrombosis to prevent thromboembolic phenomena.

Allergan Inc. (AGN), Irvine, Calif.
Ista Pharmaceuticals Inc. (ISTA), Irvine, Calif.
Business: Ophthalmic

ISTA reacquired rights to its Vitrase ovine hyaluronidase from AGN. Under a 2000 deal, AGN had worldwide rights to Vitrase outside Japan for use in the posterior segment of the eye. Now, AGN retains an option to commercialize Vitrase for the posterior segment of the eye in Europe. AGN will receive $6.5 million up front, plus an additional $3.5 million when ISTA completes a financing. AGN also is eligible for royalties.

Vitrase is approved in the U.S. as a spreading agent. In April 2003, ISTA received an approvable letter for an NDA for Vitrase to treat vitreous hemorrhage in which the agency requested an

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Merck (MRK)
Nabi (NABI)
Novartis (NVS; SWX:NOVN)
Onyx (ONXX)/Bayer (FSE:BAYG; BAY)
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Alizyme (LSE:AZM)
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Genaera (GENR)
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Kai
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ID Biomedical (IDBE; TSE:IDB)
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Solexa
Vicuron (MICU; NMerc:MICU)

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CardioVascular BioTherap
MediciNova
VASTox

Other Financial News (Page B17)

Cubist (CBST)
Genentech (DNA)
Keryx (KERX; LSE:KRX)
Nastech (NSTK)
Switch Bio
YM BioSci . (TSE:YM; LSE:YMBA)

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additional analysis of ISTA's data and a confirmatory trial based on that analysis.

Amarin Corp. plc (AMRN), London, U.K.
Valeant Pharmaceuticals International (VRX), Costa Mesa, Calif.
Business: Neurology

The companies settled their dispute regarding adjustments to the purchase price of AMRN's Amarin Pharmaceuticals Inc. unit (Mill Valley, Calif.), which VRX acquired in February *(see BioCentury, Feb. 16)*. Under the settlement, AMRN agreed to waive $6 million of the $8 million in milestones related to its Zelapar selegiline to treat Parkinson's disease (PD). VRX agreed to pay the remaining $2 million to AMRN on Nov. 30 and waived AMRN's obligation to purchase $414,000 in wholesale inventory. AMRN will pay half of the $2 million it receives from VRX to Elan Corp. plc (ELN, Dublin, Ireland) as part of a settlement related to sales milestones for Zelapar.

Applied Biosystems Group (ABI), Foster City, Calif.
Celera Genomics Group (CRA), Rockville, Md.
Genentech Inc. (DNA), South San Francisco, Calif.
Business: Cancer

The companies partnered to discover and develop targeted cancer therapeutics. CRA will nominate an undisclosed number of its cell surface antigens, and DNA may select antigens for further development. CRA is eligible for milestones and royalties. Celera Diagnostics, a joint venture between CRA and ABI, will retain certain diagnostic rights to targets selected by DNA.

Aradigm Corp. (ARDM), Hayward, Calif.
Novo Nordisk A/S (NVO), Bagsvaerd, Denmark
Business: Metabolic

ARDM granted partner NVO full development and manufacturing rights to the AERx insulin Diabetes Management System (iDMS). Under the deal, NVO will pay $55 million in cash for the manufacturing equipment and leasehold improvements used by ARDM. NVO also will assume responsibility for further development of AERx iDMS (NN1998), which is in Phase III testing. ARDM is eligible for royalties.
Under a 1998 deal, NVO had exclusive worldwide marketing rights, and ARDM was to manufacture AERx systems in exchange for a share of the gross profits on NVO's sales *(see BioCentury, June 8, 1998)*.

The partners also have an option to collaborate in specific areas, such as next-generation AERx technologies. NVO may provide certain contract manufacturing services to support other AERx programs for up to three years. ARDM has four partnered early stage AERx programs, including a Phase I study of aerosolized hydroxychloroquine (AHCQ) to treat respiratory diseases such as asthma and chronic obstructive pulmonary disease (COPD) with APT Pharmaceuticals LLC, a division of Research Corporation Technologies (Tucson, Ariz.). The company also is developing its Intraject prefilled, needle-free injection system, which it hopes to partner in 2005.

NVO said it formed a new affiliate, Novo Nordisk Delivery Technologies Inc., and that it will offer employment to about 130 ARDM employees who had been working on iDMS for ARDM.

Australian Cancer Technology Ltd. (ASX:ACU), Perth, Australia
RESprotect GmbH, Dresden, Germany
Business: Cancer

RESprotect granted ACU a North American license to RP101, a chemopotentiator that has completed a Phase I/II trial in metastatic breast, ovarian and pancreatic cancers, as well as small cell and non-small cell lung cancers. An expansion of that trial is ongoing in metastatic pancreatic cancer. RESprotect said RP101 down-regulates the oncogene STAT3 and APEX, a DNA repair gene, which are overexpressed in pancreatic cancer. ACU plans to submit an IND in 2005 and will seek Orphan Drug designation for pancreatic cancer.

Biofrontera Pharmaceuticals Holding AG, Leverkusen, Germany
DNAPrint Genomics Inc. (DNAP), Sarasota, Fla.
Business: Neurology, Dermatology, Pharmacogenetics

DNAP will invest €20 million ($24.5 million) over the next two years for a 51.4% stake in Biofrontera in the form of series B shares. The companies also entered a JV to integrate Biofrontera's drug discovery and development projects with DNAP's population genomics-based diagnostic tests for improved selection of patient groups. Biofrontera's lead program, BF-Derm1, a histidine decarboxylase inhibitor, is in Phase II studies to treat urticaria. Trial results are expected in the first quarter of 2005. DNAP's investment is secured by Dutchess Private Equities Fund, which will invest up to $35 million in DNAP shares over the next two years.

BioInvent International AB (SSE:BINV), Lund, Sweden
ThromboGenics Ltd., Dublin, Ireland
Business: Cardiovascular

BINV and ThromboGenics partnered to co-develop antibody therapeutics to treat vascular diseases. BINV will contribute its n-CoDeR antibody library, discovery and immunology technologies, and ThromboGenics will provide its research and clinical development expertise in vascular diseases. Initially, the companies will develop ThromboGenics' human anti-Factor VIII monoclonal antibody, which is in preclinical studies, as an anticoagulant to prevent and treat deep vein thrombosis (DVT) and to treat atrial fibrillation. The companies will equally share costs and revenues for new compounds and will split revenues 60/40 for candidates identified prior to the deal.

Bruker BioSciences Corp. (BRKR), Billerica, Mass.
ProteoGenix Inc., Portland, Ore.
Business: Functional genomics

The companies partnered to use ProteoGenix's protein biomarker discovery methods on the autoflex II TOF/TOF instrument from BRKR's Bruker Daltonics Inc. unit.

BTG International plc (LSE:BGC), London, U.K.
Collegium Pharmaceutical Inc., Cumberland, R.I.
University of Illinois, Chicago, Ill.
Business: Pulmonary

The companies partnered to develop a therapeutic for sleep apnea. The deal combines Collegium's formulation capabilities with BGC's undisclosed combination therapy for the indication. Separately, BGC received an exclusive license to the sleep apnea treatment from the university. BGC will fund the program, and the companies will share revenues from resulting products.

Cardiome Pharma Corp. (TSE:COM; CRME), Vancouver, B.C.
Fujisawa Pharmaceutical Co. Ltd., Tokyo, Japan
Business: Cardiovascular

COM exercised an option under the companies' 2003 deal to place US$4 million of stock with Fujisawa through the sale of about 646,000 shares at C$7.89, which is a premium of 26% to COM's Sept. 27 close of C$6.24. Last year, the companies partnered to co-develop COM's RSD1235 IV antiarrhythmic, which is in Phase III testing to treat atrial fibrillation *(see BioCentury, Oct. 20, 2003)*.

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CombinatoRx Inc., Boston, Mass.
Accelerate Brain Cancer Cure, Burlingame, Calif.
Duke University, Durham, N.C.
Business: Cancer

CombinatoRx will use its combination high throughput screening (cHTS) platform to identify combination products that hit multiple targets relevant to treating glioblastoma multiforme (GBM). The university will provide research materials and preclinical assessment of products. CombinatoRx will retain all commercial and IP rights for products discovered through the partnership and Accelerate, a nonprofit foundation, will pay CombinatoRx research funding.

Compound Therapeutics Inc., Waltham, Mass.
Abbott Laboratories (ABT), Abbott Park, Ill.
Business: Proteomics

ABT received a non-exclusive license to Compound's Profusion in vitro display technology for selecting and optimizing antibodies in the pharma company's discovery programs. Compound will receive an upfront payment and is eligible for milestones and royalties.

Corgentech Inc. (CGTK), South San Francisco, Calif.
Cyclacel Ltd., Dundee, U.K.
Business: Drug delivery

CGTK received an exclusive license to use Cyclacel's Penetratin Endonuclear Delivery System with CGTK's transcription factor decoy (TF Decoy). Penetratin is a peptide that can actively transport therapeutics into cells. TF Decoy is a class of therapeutics intended to block the activity of multiple genes linked to disease. Cyclacel received an upfront payment and is eligible for milestones and royalties. CGTK is responsible for development and commercialization of TF Decoys using penetratin peptide. CGTK's edifoligide (E2F Decoy), which does not use penetratin, is in Phase III trials to prevent bypass vein graft failure.

Exelixis Inc. (EXEL), South San Francisco, Calif.
X-Ceptor Therapeutics Inc., San Diego, Calif.
Business: Metabolic, Cardiovascular

EXEL will acquire X-Ceptor for $2.9 million in cash and 2.5 million shares. Using EXEL's Sept. 27 close of $7.77, the shares are valued at $19.4 million and the total deal value is $22.3 million. X-Ceptor is developing small molecules that target nuclear hormone receptors (NHRs) to treat metabolic and cardiovascular diseases.

X-Ceptor's lead compounds target the liver X receptor, farnesoid X receptor and mineralocorticoid receptor. EXEL expects to file INDs for certain of these programs in 2006.

Genelabs Technologies Inc. (GNLB), Redwood City, Calif.
Gilead Sciences Inc. (GILD), Foster City, Calif.
Business: Infectious

The companies partnered to identify and develop nucleoside inhibitors of HCV polymerase. GNLB will lead the research, and GILD will focus on development and commercialization. GNLB will receive an $8 million upfront payment and three years of research funding. GNLB said it could receive up to $38 million in development and regulatory milestones for each compound that is developed, plus royalties. GILD will receive exclusive worldwide rights to resulting products.

Genetic Technologies Ltd. (ASX:GTG; GNTLF), Melbourne, Australia
GenPat77 AG, Berlin, Germany
MedImmune Inc. (MEDI), Gaithersburg, Md.
Business: Autoimmune

MEDI received an exclusive license to a TIRC7 program in preclinical development from GenPat77. TIRC7 is expressed on T and B cells and is implicated in negative regulation of immune responses. The companies believe it may be useful in treating rheumatoid arthritis (RA), multiple sclerosis (MS) and other immunological diseases. MEDI will be responsible for development, manufacturing and commercialization. GenPat77 will receive an upfront payment and is eligible for milestones and royalties.

Genzyme Corp. (GENZ), Cambridge, Mass.
Business: Diagnostic

GTG granted GENZ a nonexclusive license to genetic tests in the U.S., Europe and Japan. GENZ will pay GTG $5 million in cash and grant GTG a license to GENZ's IP worth $2.5 million. GENZ also will pay GTG $1 million per year in license fees for the life of the patents, which expire in 2015.

HaptoGuard Inc., New York, N.Y.
Oxis International Inc. (OXIS), Portland, Ore.
Business: Cardiovascular

OXIS granted HaptoGuard a worldwide exclusive license to develop, manufacture and market BXT-51072 and related antioxidant compounds for various cardiovascular indications. In exchange, OXIS will receive a $450,000 license fee and is eligible for up to $21 million in milestones plus royalties. BXT-51072 is an oral glutathione peroxidase mimic that has been in Phase II testing for inflammatory bowel disease (IBD). HaptoGuard said it will begin a Phase II trial of the compound to prevent myocardial infarction (MI) in high-risk diabetic patients in the first half of next year.

ID Biomedical Corp. (TSE:IDB; IDBE), Vancouver, B.C.
National Institutes of Health, Bethesda, Md.
Business: Infectious

IDB received a $9.5 million grant from NIH to develop its cell culture-based manufacturing process as a potential replacement for egg-based production of influenza vaccines. Last month, the NIH awarded IDB up to $8 million to develop a nasally delivered plague vaccine using recombinant FIV protein formulated with the company's intranasal Proteosome adjuvant/delivery technology.

Juvaris BioTherapeutics Inc., Pleasanton, Calif.
Pennsylvania State University, University Park, Penn.
Business: Cancer

The university will test Juvaris' immunostimulation technology in rodent tumor models of acute myelogenous leukemia (AML). The parties will evaluate the antigen-specific JuvaVax AML vaccine and non-antigen JuvImmune immunostimulant for their efficacy in augmenting immune responsiveness.

Lynx Therapeutics Inc. (LYNX), Hayward, Calif.
Solexa Ltd., Cambridge, U.K.
Business: Microarrays, Chemistry, Genomics

LYNX will merge with Solexa in a stock deal. The merged company will focus on DNA sequencing technologies and expects to launch its first commercial instrument system next year. The deal combines Solexa's single molecule sequencing technology, surface chemistry, nucleotide design and informatics capabilities with LYNX's sequencing instruments. LYNX will issue about 29.5 million shares in exchange for Solexa shares. At LYNX's Sept. 28

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close of $1.91, the deal is valued at $56.3 million. Using LYNX's 7.5 million shares outstanding as of June 30, the combined company will have about 37 million shares outstanding, of which Solexa shareholders would hold 80% and LYNX shareholders would hold 20%. The new company will retain the Lynx name and ticker. Solexa CEO John West will remain CEO. The deal is expected to close by year end. Seven Hills Partners advised LYNX.

Molecular Staging Inc., New Haven, Conn.
Qiagen N.V. (FSE:QIA; QGENF), Venlo, the Netherlands
Business: Genomics, Supply/Service

QIA purchased the major assets of Molecular Staging, including its multiple displacement amplification (MDA) and rolling circle amplification (RCA) technologies, in exchange for $28.5 million in cash plus $6.8 million in sales-based milestones. QIA intends to launch a series of kits incorporating the new technologies by early 2005 and expects the transaction to add about $6 million in net sales next year. QIA said the key application of the MDA platform, licensed by Molecular Staging from Yale University (New Haven, Conn.), is a whole genome amplification technology that allows for non-specific amplification of the genome to create larger volumes of DNA for analyses from samples of limited size. Molecular Staging retains rights to its RCA technology for use in protein biomarker discovery.

Nastech Pharmaceutical Co. Inc. (NSTK), Bothell, Wash.
Thiakis Ltd., London, U.K.
Merck & Co. Inc. (MRK), Whitehouse Station, N.J.
Business: Metabolism

MRK licensed worldwide rights to co-develop NSTK's PYY3-36 to treat obesity. The nasal spray formulation of the naturally occurring PYY hormone has completed three Phase I obesity trials. NSTK will receive $5 million in cash up front and is eligible for $131 million in development and regulatory milestones plus $210 million in sales-related milestones. NSTK also is eligible for royalties.

Under the deal, the companies will jointly develop the compound, which targets the neuropeptide Y receptor. MRK will assume primary responsibility for clinical development, while NSTK will manufacture the product. MRK will lead and fund commercialization, and NSTK retained an option to co-promote PYY3-36 in the U.S. MRK also will reimburse NSTK for manufacturing-related development activities. PYY has been associated with modulation of appetite.

Separately, NSTK said it acquired from Thiakis exclusive rights to patent applications WO 03/026591 and WO 03/057235 covering peripheral delivery of PYY and the use of glucagon-like peptide-1 (GLP-1) in conjunction with PYY to treat obesity, diabetes and other metabolic conditions. The applications were submitted by Imperial College Innovations Ltd. (London, U.K.) and the Oregon Health & Science University (Portland, Ore.). NSTK made an undisclosed equity investment in Thiakis. Thiakis also will receive undisclosed license fees and is eligible for milestones and royalties.

Neurocrine Biosciences Inc. (NBIX), San Diego, Calif.
Pharmacopeia Drug Discovery Inc. (PCOP), Princeton, N.J.
Business: Neurology, Endocrine, Chemistry

PCOP received a milestone payment from NBIX under their 2003 lead identification deal *(see BioCentury, Oct. 27, 2003)*. PCOP is using its small molecule library and screening capabilities to identify lead compounds against G protein-coupled receptor (GPCR) targets selected by NBIX. The milestone was triggered by NBIX accepting compounds identified by PCOP.

Sangamo BioSciences Inc. (SGMO), Richmond, Calif.
Johnson & Johnson (JNJ), New Brunswick, N.J.
Business: Endocrine

JNJ's LifeScan Inc. unit will use SGMO's zinc finger DNA-binding proteins (ZPFs) to develop therapeutic cell lines to treat diabetes.

Spotfire Inc., Somerville, Mass.
Boehringer Ingelheim GmbH, Ingelheim, Germany
Business: Bioinformatics

Boehringer received an expanded global license to use Spotfire's Spotfire DecisionSite software for R&D activities spanning target discovery through preclinical research. Boehringer has been using DecisionSite since 1997 for genomics, lead discovery and medicinal chemistry.

Tripos Inc. (TRPS), St. Louis, Mo.
Schering AG (FSE:SCH; SHR), Berlin, Germany
Business: Bioinformatics

The partners expanded their 2001 discovery informatics deal *(see BioCentury, Sept. 10, 2001)*. The deal will include the deployment of TRPS's new Enterprise Chemical Information Management System (ECIMS), which is expected by mid-2005. TRPS will receive increased incremental funding to cover costs of completing the system, which SCH will use to manage chemical research. TRPS also is eligible for milestones.

Vernalis plc (LSE:VER; VNLS), Reading, U.K.
Cancer Research Technology Ltd., London, U.K.
The Institute of Cancer Research, London, U.K.
Business: Cancer

VER exercised its option, under a 2002 deal, to an exclusive global license for an anti-cancer Hsp90 inhibitor program from Cancer Research Technology and the institute *(see BioCentury, April 1, 2002)*. VER will pay a signature fee plus milestones, royalties and a proportion of sublicensing fees. Earlier this year, Novartis AG (NVS; SWX:NOVN, Basel, Switzerland) exercised its option to exclusively license global rights from VER to an Hsp90 oncology research program *(see BioCentury, Aug. 16)*.

Y's Therapeutics Co. Ltd., Tokyo, Japan
Kissei Pharmaceutical Co. Ltd., Nagano, Japan
Business: Antibodies, Cancer

Kissei received an option to exclusively license Japanese rights to Y's YSCMA antibody to treat cancer and immune diseases. This year, Y's hopes to begin preclinical development of the humanized monoclonal antibody against a transmembrane surface glycoprotein. The company expects to file an IND in early 2006.

SALES & MARKETING

Athena Diagnostics Inc., Worcester, Mass.
Bionomics Ltd. (ASX:BNO; BMICY), Adelaide, Australia
Business: Diagnostic

BNO granted Athena a license to market BNO's Severe Myoclonic Epilepsy of Infancy (SMEI) test for children in North America and Japan. Athena will pay BNO upfront fees, sales-related milestones and royalties.

Cepheid Inc. (CPHD), Sunnyvale, Calif.
Business: Diagnostic

CPHD launched two analyte specific reagent (ASR) primer and

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probe sets for clinical reference labs to identify Bordetella pertussis and HSV.

Connetics Corp. (CNCT), Palo Alto, Calif.
Pierre Fabre Group, Paris, France
Business: Dermatology

CNCT granted Pierre Fabre's Pierre Fabre Dermatologie unit exclusive European commercialization rights to Olux clobetasol propionate, which is approved to treat steroid responsive dermatoses of the scalp. The deal excludes Italy, but includes certain countries in South America and Africa. CNCT is eligible for milestones and royalties. Olux also is approved in the U.S. to treat mild to moderate plaque psoriasis.

Cyntellect Inc., San Diego, Calif.
Sumitomo Corp., Tokyo, Japan
Business: Biomanufacturing

Sumitomo's SC Biosciences subsidiary will market Cyntellect's Cell Xpress cell line development service in Japan. Cell Xpress uses Cyntellect's high throughput LEAP (Laser Enabled Analysis and Processing) technology for rapid cell line cloning.

Debiopharm S.A., Lausanne, Switzerland
Watson Pharmaceuticals Inc. (WPI), Corona, Calif.
Business: Cancer

Debiopharm granted WPI U.S. and Canadian marketing rights to Trelstar Depot 3.75 mg and Trelstar LA 11.25 mg. The one- and three-month sustained-release formulations of Trelstar (Decapeptyl outside the U.S.) triptorelin luteinizing hormone releasing hormone (LHRH) agonist are marketed as palliative treatments for advanced prostate cancer in the U.S. and for advanced prostate cancer and endometriosis in Canada. Debiopharm received an upfront payment from WPI.

Menarini Group, Florence, Italy
Vernalis plc (LSE:VER; VNLS), Reading, U.K.
Business: Neurology

VER partner Menarini launched VER's frovatriptan to treat migraine in Italy. Menarini will sell the drug under the names Rilamig and Auradol. Menarini already sells the drug in Germany, Ireland, the U.K., Austria and the Netherlands.

Merck & Co. Inc. (MRK), Whitehouse Station, N.J.
Business: Inflammation

MRK will withdraw its Vioxx rofecoxib COX-2 inhibitor from markets worldwide. The decision relates to data showing that Vioxx increased the risk of myocardial infarction (MI) and stroke in APPROVe, a 2,600-patient trial of Vioxx to prevent the recurrence of colorectal polyps.

MRK's other COX-2 inhibitor, Arcoxia, is approved in 47 countries outside the U.S. The company said it will work with regulatory authorities to determine whether to change the drug's label and plans to seek approval in the U.S. and elsewhere.

Vioxx was launched in 1999 and was marketed in about 80 countries. In 2003, worldwide sales of the drug were $2.5 billion, or 11% of MRK's 2003 product sales of $22.5 billion. For 2004, MRK cut its EPS guidance by $0.50-$0.60. Previously, the pharma company expected full year EPS of $3.11-$3.17.

Oscient Pharmaceuticals Corp. (OSCI), Waltham, Mass.
Business: Infectious

OSCI will add more than 150 field representatives to its sales force by early 2005 to promote Factive gemifloxacin mesylate. Factive is approved to treat acute bacterial exacerbation of chronic bronchitis (ABECB) and mild to moderate community-acquired pneumonia (CAP). Factive was launched in September with a 100-person sales force.

Schwarz Pharma AG, Monheim, Germany
Business: Neurology

Schwarz's U.S. subsidiary launched its orally dissolving Parcopa carbidopa/levodopa tablets to treat Parkinson's disease (PD). The FDA approved an ANDA for the compound in August.

OTHER NEWS

Cytogen Corp. (CYTO), Princeton, N.J.
Immunomedics Inc. (IMMU), Morris Plains, N.J.
Business: Cancer

IMMU settled its 2000 patent infringement dispute with CYTO, which alleged that CYTO's ProstaScint imaging agent infringes IMMU's U.S. Patent No. 4,460,559 covering tumor detection and localization. IMMU received an undisclosed settlement payment.

MANAGEMENT TRACKS

Boards of Directors

aaiPharma Inc. (AAII), Wilmington, N.C.
Business: Neurology, Drug delivery
Appointed: James Martin, a director and corporate VP, as non-executive chairman

Acambis plc (LSE:ACM; ACAM), Cambridge, U.K.
Business: Infectious
Appointed: Randal Chase, former president of Shire Biologics

Aphton Corp. (APHT), Miami, Fla.
Business: Cancer
Appointed: Vincent Enright, CFO of KeySpan Corp.

BioRexis Pharmaceutical Corp., King of Prussia, Penn.
Business: Endocrine
Appointed: Tom Amick, former VP of business development at Johnson & Johnson Development Corp.

Enzon Pharmaceuticals Inc. (ENZN), Bridgewater, N.J.
Business: Drug delivery, Infectious, Cancer
Appointed: Jeffrey Buchalter, president and CEO of Ilex Oncology Inc., as non-executive chairman; he succeeds Arthur Higgins, who will remain a director

Memory Pharmaceuticals Corp. (MEMY), Montvale, N.J.
Business: Neurology
Appointed: Peter Young, president and CEO of AlphaVax Inc.; he replaces Michael Sheffery, who departed

Paratek Pharmaceuticals Inc., Boston, Mass.
Business: Infectious
Appointed: Malcolm Sherman, chairman of Gordon Brothers Inc.

Santarus Inc. (SNTS), San Diego, Calif.
Business: Autoimmune, Inflammation, Metabolic
Appointed: Kent Snyder, president, CEO and director of Senomyx Inc.
Departed: Frederik Vincent van der Have

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CLINICAL NEWS

Clinical activities and selected announcements for the week ended Oct. 1.

REGULATORY

Access Pharmaceuticals Inc. (AKC), Dallas, Texas
Product: OraDisc A
Business: Dental

FDA approved an NDA for OraDisc A, a formulation of amlexanox delivered using a bioadhesive polymer, to treat aphthous ulcers in adults and children ages 12 years or older with a normal immune system.

Allergan Inc. (AGN), Irvine, Calif.
Product: Tazarotene
Business: Autoimmune

AGN received an FDA not approvable letter for oral tazarotene, an oral retinoid prodrug, to treat psoriasis. AGN said the letter listed three outstanding issues including the development of a risk management program, the completion of a non-inferiority study and satisfying an FDA deficiency letter regarding manufacturing. AGN said it is developing a risk management plan, and believes the manufacturing issue is "either resolved or will be resolved shortly." The company said it will work with FDA to clarify the request for a non-inferiority study. AGN already markets Tazorac, a topical formulation of tazarotene, to treat psoriasis and acne.

Amgen Inc. (AMGN), Thousand Oaks, Calif.
Wyeth (WYE), Madison, N.J.
Product: Enbrel etanercept
Business: Autoimmune

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Management Tracks,
from previous page

SkyePharma plc (LSE:SKP; SKYE), London, U.K.
Business: Drug delivery
Appointed: Alan Bray, retired senior partner at Deloitte & Touche LLP

Synta Pharmaceuticals Corp., Lexington, Ky.
Business: Cancer, Autoimmune
Appointed: William Reardon, former business assurance partner at PricewaterhouseCoopers

Management

aaiPharma Inc. (AAII), Wilmington, N.C.
Business: Neurology, Drug delivery
Hired: Ludo Reynders as president and CEO, formerly managing director of PharmaBio Development at Quintiles Transnational Corp.; he replaces Fred Sancillo, who retired

Applied Biosystems Group (ABI), Foster City, Calif.
Business: Supply/Service, Genomics
Promoted: Masahide Habu to president of Applied Biosystems Japan Ltd., from director of sales and marketing
Transition: Mark Stevenson to division president of Applied Markets for Applied Biosystems Group from president and general manager of Applied Biosystems Japan

Cepheid Inc. (CPHD), Sunnyvale, Calif.
Business: Microfluidics, Diagnostic, Pharmacogenetics
Hired: Emily Winn-Deen as VP of strategic planning and business development, formerly senior director for the genomics business at Roche Molecular Systems

Dynavax Technologies Corp. (DVAX), Berkeley, Calif.
Business: Infectious, Inflammation
Hired: Jane Green as VP of corporate communications, formerly VP of corporate communications at Exelixis Inc.

Hollis-Eden Pharmaceuticals Inc. (HEPH), San Diego, Calif.
Business: Drug delivery
Hired: Steven Gordziel as VP of product development, formerly VP of pharmaceutical development at Penwest Pharmaceutical Co.

Imcor Pharmaceutical Co. (ICPH), San Diego, Calif.
Business: Imaging
Departed: Brooks Boveroux as CFO and secretary; CEO Taffy Williams will serve as acting CFO

Inamed Corp. (IMDC), Santa Barbara, Calif.
Business: Dermatology
Hired: Patricia Walker as CSO and EVP for clinical and regulatory affairs, formerly VP of skin care pharmaceutical development at Allergan Inc.

Indevus Pharmaceuticals Inc. (IDEV), Lexington, Mass.
Business: Urology, Neurology, Inflammation
Hired: James Shipley as SVP of clinical development and medical affairs, formerly SVP of clinical research at Praecis Pharmaceuticals Inc.

Isolagen Inc. (ILE), Houston, Texas
Business: Dermatology
Hired: Dennis Bevan as VP of international commercial operations, formerly senior director of U.S. sales at Dermik Laboratories Inc.

Oragenics Inc. (ONI; TSE:ORA), Alachua, Fla.
Business: Dental
Hired: Edmund Mickunas as VP of regulatory and clinical affairs, formerly an industry consultant

Sidec Technologies AB, Stockholm, Sweden
Business: Proteomics
Hired: Hans Johansson as president and CEO, formerly president of the BioSystems division of Biotage AB; he replaces Goesta Sjoeholm, who resigned

Sirenade AG, Martinsried, Germany
Business: Neurology
Hired: Lynn Butler as CEO, formerly director of Swentibold sprl; she replaces interim CEO Pierfausto Seneci, who becomes CSO

Trubion Pharmaceuticals Inc., Seattle, Wash.
Business: Inflammation, Cancer
Hired: Judith Woods as VP of legal affairs and chief patent counsel, formerly associate general counsel for IP at Abgenix Inc.

Regulatory,
from previous page

WYE received EU approval for Enbrel etanercept, a TNF alpha inhibitor, to treat moderate to severe plaque psoriasis in adults who failed to respond to, have a contraindication to or are intolerant of other systemic therapy.

Axcan Pharma Inc. (TSE:AXP; AXCA), Mont St. Hilaire, Quebec
Product: Photofrin porfimer sodium
Business: Cancer

EMEA granted Orphan Drug designation to Photofrin porfimer, a photosensitizing agent used in photodynamic therapy (PDT), to treat cholangiocarcinoma.

Biogen Idec Inc. (BIIB), Cambridge, Mass.
Elan Corp. plc (ELN), Dublin, Ireland
Product: Antegren natalizumab
Business: Autoimmune

ELN and BIIB submitted an MAA to EMEA for Antegren to treat Crohn's disease. The humanized monoclonal antibody against integrin alpha(4) is under review to treat multiple sclerosis (MS) in the EU, Canada and U.S., where it has Priority Review and Accelerated Approval designations.

Biomira Inc. (TSE:BRA; BIOM), Edmonton, Alberta
Merck KGaA (FSE:MRK), Darmstadt, Germany
Product: BLP25
Business: Cancer

FDA granted Fast Track designation to BLP25 liposome vaccine to treat non-small cell lung cancer (NSCLC).

Chiron Corp. (CHIR), Emeryville, Calif.
Gen-Probe Inc. (GPRO), San Diego, Calif.
Product: Procleix Ultrio assay
Business: Diagnostic

GPRO and CHIR submitted a BLA for the Procleix Ultrio blood screening assay for simultaneous detection of HIV-1, HCV and HBV in donated blood, plasma, organs and tissues.

Enzon Pharmaceuticals Inc. (ENZN), Bridgewater, N.J.
Inex Pharmaceuticals Corp. (TSE:IEX), Burnaby, B.C.
Product: Marqibo vincristine
Business: Cancer

The partners said FDA's Oncologic Drugs Advisory Committee will review an NDA for Marqibo to treat relapsed, aggressive non-Hodgkin's lymphoma (NHL) previously treated with at least two combination chemotherapy regimens. The NDA has a PDUFA date of Jan. 15, 2005, and is scheduled for review on Dec.1. ENZN has exclusive North American rights to the Transmembrane Carrier System (TCS) liposomal formulation of vincristine.

Genentech Inc. (DNA), South San Francisco, Calif.
OSI Pharmaceuticals Inc. (OSIP), Melville, N.Y.
Roche (SWX:ROCZ), Basel, Switzerland
Product: Tarceva erlotinib
Business: Cancer

FDA accepted for filing an NDA for Tarceva as monotherapy to treat advanced non-small cell lung cancer (NSCLC) in patients who have failed chemotherapy. The small molecule inhibitor of epidermal growth factor (EGF) receptor also has been granted priority review classification by FDA.

Gentium S.p.A., Como, Italy
Product: Defibrotide
Business: Hepatic

EMEA granted Orphan Drug designation to defibrotide, a mixture of single-stranded oligodeoxyribonucleotides derived from porcine mucosal DNA, to treat and prevent hepatic veno-occlusive disease.

GlaxoSmithKline plc (GSK; LSE:GSK), London, U.K.
Product: Mepolizumab
Business: Hematology

EMEA granted Orphan Drug designation to mepolizumab, a monoclonal antibody against IL-5, to treat hypereosinophilic syndrome, a high, persistent eosinophil count.

Guilford Pharmaceuticals Inc. (GLFD), Baltimore, Md.
Product: Gliadel Wafer
Business: Cancer

FDA granted Orphan Drug designation to Gliadel wafer carmustine implant to treat patients with malignant glioma undergoing primary surgical resection.

Innate Pharma S.A.S., Marseille, France
Product: Phosphostim
Business: Cancer

EMEA granted Orphan Drug designation to Phosphostim, a small non-peptidic synthetic molecule that activates lymphocytes, to treat renal cell carcinoma.

Johnson & Johnson (JNJ), New Brunswick, N.J.
Schering-Plough Corp. (SGP), Kenilworth, N.J.
Product: Remicade infliximab
Business: Autoimmune

FDA approved an sBLA for Remicade in combination with methotrexate as a first line regimen to treat moderate to severe rheumatoid arthritis (RA). The anti-TNF alpha antibody, which is marketed in Europe by SGP and in the U.S. by JNJ subsidiary Centocor Inc. (Malvern, Pa.), already is approved to treat RA and Crohn's disease.

Kai Pharmaceuticals Inc., South San Francisco, Calif.
Product: KAI-9803
Business: Cardiovascular

FDA granted Fast Track designation to KAI-9803, a PKC inhibitor, to reduce reperfusion injury as an adjunct to current treatments for acute myocardial infarction (MI).

Les Laboratories Servier, Paris, France
Product: Protelos strontium ranelate
Business: Musculoskeletal

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BioCentury Part II

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EMEA granted marketing authorization for Protelos, an agent that increases bone formation and decreases bone resorption, to treat postmenopausal osteoporosis.

Lynkeus BioTech GmbH, Wurzburg, Germany
Product: LYN001
Business: Ophthalmic

Lynkeus received Orphan Drug designation in Europe for its LYN001 peptide to treat autoimmune uveitis.

MGI Pharma Inc. (MOGN), Minneapolis, Minn.
SuperGen Inc. (SUPG), Dublin, Calif.
Product: Dacogen decitabine
Business: Cancer

The companies submitted an MAA to the EMEA for Dacogen to treat patients with myelodysplastic syndromes (MDS). The companies expect to complete a rolling NDA submission for the hypomethylating agent this quarter. Last month, MOGN received exclusive worldwide rights from SUPG to develop, manufacture and market Dacogen.

Millennium Pharmaceuticals Inc. (MLNM), Cambridge, Mass.
Johnson & Johnson (JNJ), New Brunswick, N.J.
Product: Velcade bortezomib
Business: Cancer

MLNM submitted an sNDA to FDA for Velcade bortezomib, a small molecule dipeptide boronic acid proteasome inhibitor, to treat multiple myeloma (MM) in patients who have received at least one prior therapy.

NovaDel Pharma Inc. (NVD), Flemington, N.J.
Product: Nitroglycerin lingual spray
Business: Cardiovascular

FDA accepted for review an NDA for NVD's nitroglycerin lingual spray for the acute relief of an attack, or acute prophylaxis of angina pectoris due to coronary artery disease (CAD). The NDA has a PDUFA date of June 4, 2005. Par Pharmaceuticals Companies Inc. (PRX, Spring Valley, N.Y.) has exclusive rights to market, sell and distribute the lingual spray in the U.S. and Canada.

Novartis AG (NVS; SWX:NOVN), Basel, Switzerland
Product: Midostaurin (PKC412)
Business: Cancer

EMEA granted Orphan Drug designation to NVS subsidiary Novartis Europharm Ltd. (West Sussex, U.K.) for midostaurin, a protein kinase C (PKC) inhibitor, to treat acute myeloid leukemia (AML).

Otsuka Pharmaceutical Co. Ltd., Tokyo, Japan
Bristol-Myers Squibb Co. (BMY), New York, N.Y.
Product: Abilify aripiprazole
Business: Neurology

FDA granted marketing approval for Abilify to treat acute bipolar mania, including manic and mixed episodes associated with bipolar disorder. BMY markets the once-daily small molecule partial agonist of dopamine D2 receptors in the U.S. and EU to treat schizophrenia.

Protein Design Labs Inc. (PDLI), Fremont, Calif.
Product: Nuvion visilizumab
Business: Autoimmune

FDA granted Fast Track designation to visilizumab, a humanized monoclonal antibody against CD3, to treat corticosteroid-refractory ulcerative colitis.

Purdue Pharma L.P., Stamford, Conn.
Product: Palladone
Business: Neurology

FDA approved an NDA for Palladone hydromorphone extended-release capsules to manage persistent, moderate to severe pain in patients requiring continuous, around-the-clock analgesia with a high potency opioid for an extended period of time. Palladone is expected to be available in the U.S. in the first half of 2005 and already is marketed in Canada, the U.K. and Germany.

Schwarz Pharma AG, Monheim, Germany
Product: Neupro
Business: Neurology

Schwarz submitted an NDA to FDA for Neupro, a dopamine D2 receptor agonist patch, to treat Parkinson's disease (PD). Separately, Schwarz submitted an MAA to EMEA in the same indication.

Trinity Biotech plc (TRIB), Dublin, Ireland
Product: Uni-Gold Recombigen HIV test
Business: Diagnostic

FDA granted marketing approval for the Uni-Gold Recombigen HIV Test with finger stick whole blood samples. The test already is marketed to detect antibodies to HIV in human serum, plasma or whole blood *(see BioCentury, Jan. 5).*

ZymoGenetics Inc. (ZGEN), Seattle, Wash.
Novo Nordisk A/S (NVO), Bagsvaerd, Denmark
Product: Interleukin-21 (IL-21)
Business: Cancer

EMEA granted Orphan Drug designation to recombinant human IL-21 to treat renal cell carcinoma.

CLINICAL RESULTS

Amgen Inc. (AMGN), Thousand Oaks, Calif.
Nuvelo Inc. (NUVO), Sunnyvale, Calif.
Product: Alfimeprase
Business: Cardiovascular
Molecular target: Fibrin
Description: Modified fibrolase
Indication: Treat acute peripheral arterial occlusions (leg attack)
Endpoint: Adverse event (AE) rate, serious adverse event (SAE) rate, and major bleeding including intracerebral hemorrhage (ICH) up to 30 days after dosing; determination of alfimeprase activity, open-surgery free survival at 14 and 30 days, patency
Status: Phase II data
Milestone: NA

In the open-label, dose-escalation, international Phase II NAPA-1 trial in 113 patients, alfimeprase restored arterial flow up to 60% within 4 hours of initiation of dosing. There were no deaths or ICH. Data were presented at the Transcatheter Cardiovascular Therapeutics Symposium in Washington.

Angiotech Pharmaceuticals Inc. (TSE:ANP; ANPI), Vancouver, B.C.
Boston Scientific Corp. (BSX), Natick, Mass.
Product: Taxus
Business: Cardiovascular
Molecular target: Tubulin
Description: Coronary stent coated with slow-release paclitaxel
Indication: Treat restenosis
Endpoint: Target vessel revascularization (TVR), target lesion revascularization (TLR), in-segment binary restenosis

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Status: Pivotal trial data
Milestone: NA

Two-year data from the double-blind, U.S. TAXUS IV trial in 1,326 patients showed that the TLR rate in the paclitaxel-eluting stent group was 5.6% compared to 17.5% in the control group. Data were presented at the Transcatheter Cardiovascular Therapeutics symposium in Washington.

Indication: Treat restenosis
Endpoint: Percent in-stent volume obstruction as assessed by intravascular ultrasound (IVUS)
Status: Pivotal trial data
Milestone: NA

Two-year data from the double-blind, international TAXUS II trial in 536 patients showed that the target lesion revascularization (TLR) rate for patients receiving the slow-release and moderate-release stents was 5.5% and 3.9%, respectively, a signficant difference compared to the TLR rate of 15.5% for control patients. Data were presented at the Transcatheter Cardiovascular Therapeutics symposium in Washington.

Ariad Pharmaceuticals Inc. (ARIA), Cambridge, Mass.
Product: AP23573
Business: Cancer
Molecular target: FK 506 binding protein (FKBP-12, macrophilin-12)
Description: Small molecule mTOR inhibitor
Indication: Treat relapsed and/or refractory cancer
Endpoint: Safety; immune response
Status: Phase I data
Milestone: NA

In 2 open-label, U.S. Phase I trials, 49% of the patients had anti-tumor responses with a median duration of response of 5 months. Nine of 49 evaluable patients had tumor regression and 15 had disease stabilization. Data were presented at the European Organization for Research and Treatment of Cancer - National Cancer Institute - American Association for Cancer Research (EORTC-NCI-AACR) meeting in Geneva.

ArQule Inc. (ARQL), Woburn, Mass.
Product: ARQ501
Business: Cancer
Molecular target: NA
Description: Activated Checkpoint Therapy (ACT) platform compound
Indication: Treat refractory solid tumors
Endpoint: NA
Status: Phase I interim data
Milestone: NA

Interim results from an open-label Phase I trial showed 3 of 14 evaluable patients had disease stabilization. Data were presented at the European Organization for Research and Treatment of Cancer - National Cancer Institute - American Association for Cancer Research (EORTC-NCI-AACR) meeting in Geneva.

AtheroGenics Inc. (AGIX), Alpharetta, Ga.
Product: AGI-1067
Business: Cardiovascular
Molecular target: NA
Description: Small molecule that blocks vascular cell adhesion molecule-1 (VCAM-1) expression
Indication: Treat coronary atherosclerosis
Endpoint: Change in total plaque volume after 12-month period compared to baseline; change in plaque volume from baseline
Status: Phase IIb interim data
Milestone: Phase IIb final data (year end 2004)

Interim data from 133 patients in the placebo-controlled Phase IIb CART-2 trial showed AGI-1067 significantly reduced coronary atherosclerosis from baseline, as measured by a decrease in plaque volume ($p<0.0003$). Plaque volume was reduced by an average of 6.4 mm^3, which was a 3.8% decrease. Compared with placebo, AGI-1067 gave larger reductions in plaque volume, but the differences were not significant, which AGIX said reflects the small number of patients in the interim analysis. In the subsegment of each patient's most severely diseased artery, AGI-1067 also significantly reduced plaque volume from baseline, a secondary endpoint ($p<0.0001$). In these segments, the average reduction was 2.7 mm^3 (7.1%). All patients received standard care, and changes in plaque volume were measured using intravascular ultrasound (IVUS). Final top-line data from CART-2 are expected this year. AGI-1067 is in a Phase III trial (ARISE) for the secondary prevention of coronary artery disease (CAD).

Biocompatibles International plc (LSE:BII), Farnham, U.K.
Product: Drug-Eluting Bead (DEB)
Business: Cancer
Molecular target: NA
Description: Drug delivery device that uses the N-fil Technology (embolic microspheres)
Indication: Treat liver cancer
Endpoint: Treatment-related complications; tumor response at 6 months
Status: Phase I/II preliminary data
Milestone: NA

Preliminary results from the Chinese and Spanish Phase I/II PRECISION trial in 60 patients showed that only 10% of patients treated with DEB experienced treatment-related complications compared to 27.5% of those receiving the standard therapy of a TACE (trans arterial chemo embolization) procedure. The product has CE mark approval in Europe. Data were presented at the Cardiovascular and Interventional Radiological Society of Europe meeting in Barcelona.

Biogen Idec Inc. (BIIB), Cambridge, Mass.
Elan Corp. plc (ELN), Dublin, Ireland
Product: Antegren natalizumab
Business: Autoimmune
Molecular target: Integrin alpha(4)
Description: Humanized monoclonal antibody against integrin alpha(4)
Indication: Treat moderate to severe Crohn's disease
Endpoint: CDAI score of <220 and <70-point increase from baseline without any rescue medication intervention throughout study period
Status: Phase III data
Milestone: NA

Twelve-month results from the double-blind international Phase III ENACT-2 trial in 339 patients showed that 54% of patients treated with Antegren had a sustained response compared to 20% of those in the placebo group. Also, 39% of patients treated with Antegren maintained a clinical remission compared to 15% in the placebo group. Data were presented at the United European Gastroenterology Week meeting in Prague.

BioXell SpA, Milan, Italy
Product: BXL-628

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Clinical Results,
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Business: Genitourinary
Molecular target: NA
Description: Vitamin D3 analog that inhibits keratinocyte growth factor (KGF) and insulin-like growth factor-1 (IGF-1)
Indication: Treat benign prostatic hyperplasia (BPH)
Endpoint: Prostate volume reduction
Status: Phase IIa data
Milestone: Start Phase IIb (early 2005)

In a 12-week, double-blind Phase IIa trial in 120 patients, BXL-628 reduced prostate volume by 7.2% compared to placebo ($p<0.0001$). The prostate grew by 4.3% in the placebo group and shrank by 2.9% in the BXL-628 group. Also, 92% of patients receiving BXL-628 did not have clinically significant growth in prostate volume compared to 48% of patients given placebo ($p<0.0001$).

Clavis Pharma AS, Oslo, Norway
Product: CP-4055
Business: Cancer
Molecular target: NA
Description: Fatty acid derivative of cytarabine
Indication: Treat solid tumor in patients with advanced malignant melanoma, lung cancer or ovarian cancer
Endpoint: Maximum tolerated dose, dose-limiting toxicity, safety; pharmacokinetics
Status: Phase I preliminary data
Milestone: Start Phase II (2005)

Preliminary data from an open-label, European Phase I trial in 24 patients showed tumor growth cessation in 8 patients.

Enzo Biochem Inc. (ENZ), Farmingdale, N.Y.
Product: Alequel
Business: Autoimmune
Molecular target: NA
Description: Autologous colon-derived antigens
Indication: Treat Crohn's disease
Endpoint: Not disclosed
Status: Phase II data
Milestone: NA

In a double-blind, placebo-controlled Phase II trial in 26 evaluable patients, 67% of those given Alequel had a clinical response compared to 43% of patients in the placebo group. Also, 58% of Alequel patients achieved clinical remission compared with 29% of placebo-treated subjects.

Guidant Corp. (GDT), Indianapolis, Ind.
Product: Everolimus-eluting coronary stent
Business: Cardiovascular
Molecular target: NA
Description: Everolimus-eluting coronary stent system utilizing a durable polymer
Indication: Treat coronary artery disease (CAD)
Endpoint: Angiographic in-stent late loss at 6 months
Status: NA data
Milestone: NA

In the single-blind, European SPIRIT FIRST study in 60 patients, the in-stent late loss at 6 months was 0.10 mm for patients receiving the Multi-link Vision-based everolimus-eluting stent compared to 0.84 mm those receiving the non-eluting Multi-link Vision stent. Data were presented at the Cardiovascular Research Foundation's Scientific Symposium in Washington.

Human Genome Sciences Inc. (HGSI), Rockville, Md.
Product: HGS-ETR1
Business: Cancer
Molecular target: Tumor necrosis factor related apoptosis inducing ligand receptor-1 (TRAIL-R1)
Description: TRM-1 antibody agonist of Tumor necrosis factor related apoptosis inducing ligand receptor-1 (TRAIL-R1)
Indication: Treat advanced solid malignancies
Endpoint: Safety, maximum tolerated dose and dose-limiting toxicities; tumor response
Status: Phase I data
Milestone: NA

In an ongoing, open-label, dose-escalation, U.S. Phase I trial in 39 patients, HGS-ETR1 treatment was reported to be safe at doses up to and including 10 mg/kg. Data were presented at the European Organization for Research and Treatment of Cancer - National Cancer Institute - American Association for Cancer Research (EORTC-NCI-AACR) meeting in Geneva.

Indication: Treat advanced solid malignancies
Endpoint: Safety; pharmacokinetics and tumor response
Status: Phase I data
Milestone: NA

In an ongoing, open-label, dose-escalation, Canadian Phase I trial in 24 patients, HGS-ETR1 was well tolerated. Data were presented at the European Organization for Research and Treatment of Cancer - National Cancer Institute - American Association for Cancer Research (EORTC-NCI-AACR) meeting in Geneva.

Product: HGS-ETR2
Business: Cancer
Molecular target: Tumor necrosis factor related apoptosis inducing ligand receptor-1 (TRAIL-R1)
Description: Human monoclonal antibody against tumor necrosis factor related apoptosis inducing ligand receptor-2 (TRAIL-R2)
Indication: Treat advanced solid tumors
Endpoint: Safety; pharmacokinetics and disease response
Status: Phase I data
Milestone: NA

In an ongoing, open-label, dose-escalation, U.K. Phase I trial in 18 patients, HGS-ETR2 treatment was safe and well tolerated. Data were presented at the European Organization for Research and Treatment of Cancer - National Cancer Institute - American Association for Cancer Research (EORTC-NCI-AACR) meeting in Geneva.

Johnson & Johnson (JNJ), New Brunswick, N.J.
Product: Eprex epoetin alfa
Business: Hematology
Molecular target: Erythropoietin (EPO) receptor
Description: Recombinant erythropoietin alfa (EPO)
Indication: Treat anemia in patients with chronic kidney disease (CKD)
Endpoint: NA
Status: NA
Milestone: NA

Reasearchers published that the worldwide incidence of epoetin-associated, antibody-mediated pure red-cell aplasia (PRCA) has decreased by 83% since 2001 because of procedures that were adopted to ensure appropriate storage, handling and administration of Eprex. In particular, the researchers noted that in 2002 several major health agencies in Europe concluded that subcutaneous Eprex should be considered contraindicated in patients with CKD and mandated the use of IV Eprex. Between 2001 and 2003,

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Clinical Results,
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the estimated exposure-adjusted incidence of PRCA was 18 cases per 100,000 patient-years for Eprex formulated without human serum albumin, 6 per 100,000 patient years for Eprex formulated with human serum albumin, 1 case per 100,000 patient years for Neorecormon epoetin beta from Roche (SWX:ROCZ, Basel, Switzerland), and 0.2 cases per 100,000 patient years for Epogen epoetin alfa from Amgen (AMGN, Thousand Oaks, Calif.). Data were published in *The New England Journal of Medicine.*

Keryx Biopharmaceuticals Inc. (KERX; LSE:KRX), New York, N.Y.
Product: Perifosine (KRX-0401)
Business: Cancer
Molecular target: NA
Description: Alkylphosphocholine compound that inhibits Akt signaling
Indication: Treat advanced soft tissue sarcoma
Endpoint: NA
Status: Phase II data
Milestone: NA

In a Phase II trial in 23 patients, one patient had a confirmed partial response lasting more than 5 months and 2 remained progression-free at 6 months. KRX-0401 was well tolerated at the doses used. Data were presented at the European Organization for Research and Treatment of Cancer - National Cancer Institute - American Association for Cancer Research (EORTC-NCI-AACR) meeting in Geneva.

Lorus Therapeutics Inc. (TSE:LOR; LRP), Toronto, Ontario
Product: GTI 2040
Business: Cancer
Molecular target: Ribonucleotide reductase mRNA
Description: Antisense compound against ribonucleotide reductase R2 subunit
Indication: Treat metastatic renal cell cancer
Endpoint: NA
Status: Phase II interim data
Milestone: Complete Phase II (year end 2004)

Interim data from an open-label, U.S. Phase II trial in 29 patients showed that 50% of patients getting GTI 2040 in combination with capecitabine had disease stabilization. The combination was well tolerated. Data were presented at the European Organization for Research and Treatment of Cancer - National Cancer Institute - American Association for Cancer Research (EORTC-NCI-AACR) meeting in Geneva.

Merck & Co. Inc. (MRK), Whitehouse Station, N.J.
Product: Cancidas caspofungin
Business: Infectious
Molecular target: Beta 1,3-D-glucan synthase
Description: Inhibitor of beta 1,3-D-glucan in fungal cell walls
Indication: Treat fungal infection
Endpoint: Overall response
Status: Phase III data
Milestone: NA

In a double-blind, international Phase III trial in 1,095 patients, caspofungin was non-inferior to liposomal amphotericin. Specifically, 33.9% of patients who received caspofungin had an overall response compared to 33.7% of patients who received amphotericin. The proportion of patients who survived at least 7 days after therapy was greater in the caspofungin group (92.6% vs. 89.2%, p=0.05). Results were published in *The New England Journal of Medicine.*

Product: Vioxx rofecoxib
Business: Cancer
Molecular target: Cyclooxygenase-2 (COX-2)
Description: Cyclooxygenase-2 (COX-2) inhibitor
Indication: Prevent recurrence of colorectal polyps in patients with a history of colorectal adenomas
Endpoint: NA
Status: NA
Milestone: NA

In the 3-year, double-blind, placebo-controlled APPROVe trial in 2,600 patients, 15 patients per 1,000 given 25 mg of Vioxx had a confirmed cardiovascular event, compared to 7.5 patients per 1,000 given placebo. MRK said the increased risk began after 18 months and was not seen during the first 18 months of the trial. Based on the results of the trial, MRK has voluntarily withdrawn the drug from the market worldwide.

Nabi Biopharmaceuticals (NABI), Boca Raton, Fla.
Product: NicVax
Business: Neurology
Molecular target: NA
Description: Nicotine conjugate vaccine
Indication: Treat and prevent nicotine addiction
Endpoint: Safety, immune response
Status: Phase II data
Milestone: NA

In a double-blind, placebo-controlled, U.S. Phase II trial in 68 smokers, 200 µg NicVAX gave a 33% quit rate vs. 9% for placebo. Patients were given 1 of 3 doses of NicVax (50, 100 or 200 µg) or placebo on days 0, 28, 56 and 182.

Novartis AG (NVS; SWX:NOVN), Basel, Switzerland
Product: Gleevec (Glivec - EU) imatinib
Business: Cancer
Molecular target: NA
Description: 2-phenylaminopyrimidine derivative that inhibits tyrosine kinase domains of multiple receptors
Indication: Treat metastatic gastrointestinal stromal tumor (GIST)
Endpoint: Progression-free survival; overall survival, response to treatment, toxic effects
Status: Phase III data
Milestone: NA

In an open-label, international Phase III trial in 946 patients, Gleevec 400 mg twice daily significantly improved progression-free survival compared to Gleevec 400 mg once daily (p=0.026). Side effects were more common and severe with the higher dose, and the majority of patients required treatment interruption due to adverse events. Results were published in *The Lancet*.

Indication: Treat dermatofibrosarcoma protuberans (DFSP)
Endpoint: Objective response rate; safety
Status: Phase II data
Milestone: NA

In an open-label, international Phase II trial in 10 patients, 800 mg of Gleevec daily alone or in combination with surgery gave complete disease control in 8 patients. Results were presented at the European Organisation for Research and Treatment of Cancer - National Cancer Institute - American Association for Cancer Research meeting (EORTC-NCI-AACR) in Geneva.

Onyx Pharmaceuticals Inc. (ONXX), Richmond, Calif.
Bayer AG (FSE:BAYG; BAY), Leverkusen, Germany

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Clinical Results,
from previous page

Product: BAY 43-9006
Business: Cancer
Molecular target: Raf
Description: Oral small molecule inhibitor of Raf and other kinases
Indication: Treat advanced inoperable primary liver cancer
Endpoint: N/A
Status: Phase II preliminary data
Milestone: Start Phase III (1H05)

Preliminary data from an international Phase II trial in 137 patients showed that 43% of patients treated with BAY 43-9006 experienced stable disease for at least 4 months, and 9% experienced tumor shrinkage. The trial was open-label for the first 12 weeks followed by a placebo-controlled portion for those patients with stable disease. Data were presented at the American Association for Cancer Research — National Cancer Institute — European Organization for Research and Treatment of Cancer (AACR-NCI-EORTC) meeting in Geneva.

Oscient Pharmaceuticals Corp. (OSCI), Waltham, Mass.
Product: Factive gemifloxacin
Business: Infectious
Molecular target: DNA gyrase; Topoisomerase IV
Description: Antibacterial agent gemifloxacin mesylate
Indication: Treat acute bacterial rhinosinusitis
Endpoint: Eradication or presumed eradication of all initial pathogens without any new infections
Status: Phase III data
Milestone: NA
In a double-blind Phase III trial in 216 evaluable patients, 90.3% of those given a 5-day Factive treatment had eradication or presumed eradication of initial pathogens without new infection at follow-up, the primary endpoint. Data were presented at the Infectious Disease Society of America meeting in Boston.

Indication: Treat acute bacterial rhinosinusitis
Endpoint: Clinical success, sufficient improvement or resolution of symptoms
Status: Phase III data
Milestone: NA
In a double-blind Phase III trial in 356 per-protocol patients, 87.3% and 86.9% of those given Factive for 5 and 7 days, respectively, showed clinical success, sufficient improvement or resolution of symptoms, the primary endpoint. Data were presented at the Infectious Disease Society of America meeting in Boston.

Protein Design Labs Inc. (PDLI), Fremont, Calif.
Product: Anti-a5B1 (M200)
Business: Cancer
Molecular target: Integrin alpha(5)beta(1)
Description: Anti-endothelial cell antibody that inhibits angiogenesis
Indication: Treat refractory solid tumors
Endpoint: Safety
Status: Phase I interim data
Milestone: Start Phase II (4Q04)

Interim results from a dose-escalation Phase I trial in 16 patients showed that M200 was well tolerated. Ten of 15 evaluable patients had stable disease. Data were presented at the European Organization for Research and Treatment of Cancer - National Cancer Institute - American Association for Cancer Research (EORTC-NCI-AACR) meeting in Geneva.

Product: Nuvion visilizumab
Business: Autoimmune
Molecular target: CD3
Description: Humanized monoclonal antibody against CD3
Indication: Treat severe ulcerative colitis refractory to intravenous steroids
Endpoint: Reduction in Modified Truelove and Witts Severity Index (MTWSI) score, safety
Status: Phase I/II interim data
Milestone: Phase I/II data (2H05)

Thirty-day interim data from an international Phase I/II trial in 50 evaluable patients showed that 87% of patients achieved a clinical response and 27% achived remission as measured by MTWSI score. Also, 63% of patients showed an improvement in mucosal score as measured by flexible sigmoidoscopy. Data were presented at the United European Gastroenterology Week meeting in Prague.

Valentis Inc. (VLTS), Burlingame, Calif.
Product: Deltavasc
Business: Cardiovascular
Molecular target: NA
Description: Cationic lipid delivery of plasmid encoding the developmentally-regulated endothelial locus-1 (Del-1) gene that stimulates angiogenesis and inhibits endothelial cell death
Indication: Treat intermittent claudication form of peripheral arterial disease (PAD)
Endpoint: Safety and change in exercise tolerance after 90 days
Status: Phase II data
Milestone: NA

In a double-blind, placebo-controlled, U.S. Phase II trial in 100 patients, Deltavasc plus PINC polymer failed to improve the primary endpoint of exercise tolerance compared to patients given the polymer alone. In both groups, exercise tolerance significantly increased from baseline ($p=0.0001$ and $p<0.00001$, respectively). The company plans to start a trial of Deltavasc in a non-cardiovascular indication and said it will continue to evaluate "opportunities" for the compound in cardiovascular indications.

CLINICAL STATUS

Alizyme plc (LSE:AZM), Cambridge, U.K.
Product: ATL-962
Business: Endocrine
Molecular target: Lipase
Description: Lipase inhibitor
Indication: Treat obesity in patients with diabetes
Endpoint: Weight loss
Status: Phase IIb start
Milestone: Phase IIb data (year end 2005)

AZM will begin this month a double-blind, European Phase IIb trial comparing 3 doses of ATL-962 with placebo and Xenical in up to 600 patients with a body mass index (BMI) of more than 28. Xenical orlistat is marketed by Roche (SWX:ROCZ, Basel, Switzerland).

Ariad Pharmaceuticals Inc. (ARIA), Cambridge, Mass.
Product: AP23573
Business: Cancer
Molecular target: FK 506 binding protein (FKBP-12, macrophilin-12)
Description: Small molecule mTOR inhibitor
Indication: Treat solid tumors in patients with bone and soft tissue sarcomas
Endpoint: Response rate

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Clinical Status,
from previous page

Status: Phase II started
Milestone: NA

ARIA began an open-label, U.S. and European Phase II trial in up to 175 patients.

BTG plc (LSE:BGC), London, U.K.
Product: Varisolve
Business: Cardiovascular
Molecular target: NA
Description: Varisolve endovenous microfoam for sclerotherapy
Indication: Treat varicose veins
Endpoint: NA
Status: NA
Milestone: NA

BGC said the data it has generated do not support the submission of a complete response to FDA's clinical hold, which the company previously anticipated submitting by the end of next month. In November 2003, FDA placed a clinical hold on Varisolve due to concerns about the potential risks of gas embolism. BGC said its Provensis Ltd. subsidiary has reformulated Varisolve and has conducted in vitro and preclinical studies as well as a clinical study to generate the information required by the FDA. Provensis plans to repeat one of the preclinical studies, with interim findings anticipated in January 2005. If positive, the second part of the study will be conducted and Provensis will then assess whether the total data package supports submission of a response to the clinical hold, potentially by mid-2005.

Cardiome Pharma Corp. (TSE:COM; CRME), Vancouver, B.C.
Product: RSD1235
Business: Cardiovascular
Molecular target: NA
Description: Mixed ion channel antagonist
Indication: Treat acute atrial fibrillation
Endpoint: Safety and pharmacokinetics
Status: Phase I started
Milestone: Preliminary Phase I data (year end 2004); final Phase I data (2005)

CRME began an open-label, crossover, Dutch Phase I trial in 12 patients to compare 2 controlled-release formulations of oral RSD1235 with an immediate-release formulation.

Connetics Corp. (CNCT), Palo Alto, Calif.
Product: Desilux desonide
Business: Dermatology
Molecular target: NA
Description: Low-potency topical steroid, formulated with 0.05% desonide in emollient foam delivery vehicle
Indication: Treat atopic dermatitis
Endpoint: NA
Status: Phase III started
Milestone: Submit NDA (year end 2005)

CNCT began a Phase III trial in patients aged 3 months to 17 years.

DOV Pharmaceutical Inc. (DOVP), Hackensack, N.J.
Product: Bicifadine
Business: Neurology
Molecular target: NA
Description: Norepinephrine and serotonin agonist and calcium channel blocker
Indication: Treat moderate to severe chronic lower back pain
Endpoint: Change in pain severity ratings, measures of functional disability and patients' global impression of change from baseline
Status: Phase III started
Milestone: NA

DOVP began a double-blind, placebo-controlled, U.S. Phase III trial in about 600 patients. The trial has an SPA.

Epimmune Inc. (EPMN), San Diego, Calif.
Product: EP-2101
Business: Cancer
Molecular target: NA
Description: Multi-epitope cancer vaccine
Indication: Treat stage IIIB/IV non-small cell lung cancer (NSCLC)
Endpoint: Overall survival, safety; progression-free survival and vaccine immunogenicity
Status: Phase II start
Milestone: Complete enrollment Phase II (year end 2005); Phase II data (2H06)

EPMN will begin this month an open-label, U.S. Phase II trial in about 84 patients.

Genaera Corp. (GENR), Plymouth Meeting, Penn.
Product: Squalamine
Business: Ophthalmic
Molecular target: Calmodulin
Description: Synthetic anti-angiogenic aminosterol that inhibits endothelial cell migration and proliferation
Indication: Treat wet age-related macular degeneration (AMD)
Endpoint: Safety; visual acuity
Status: Phase II started
Milestone: NA

GENR began the U.S. Phase II MSI-1256F-208 study in 45 patients who will receive 1 of 3 different doses (10, 20 or 40 mg) of squalamine in combination with an initial Visudyne treatment.

Immtech International Inc. (IMM), Vernon Hills, Ill.
Product: DB-289
Business: Infectious
Molecular target: DNA
Description: Binder of parasite DNA that competes with binding of topoisomerase II
Indication: Treat African sleeping sickness (trypanosomiasis)
Endpoint: NA
Status: Phase IIb completed enrollment
Milestone: NA

IMM completed enrollment of 30 patients in the extended dose regimen arm of an open-label, African Phase IIb trial.

Kai Pharmaceuticals Inc., South San Francisco, Calif.
Product: KAI-9803
Business: Cardiovascular
Molecular target: Protein kinase C (PKC)
Description: Protein kinase C (PKC) delta inhibitor
Indication: Treat reperfusion injury
Endpoint: Safety; clinical outcome
Status: Phase I/II started
Milestone: NA

Kai began a dose-escalation, double-blind, placebo-controlled, U.S. Phase I/II trial in 150 patients undergoing urgent angioplasty.

Medarex Inc. (MEDX), Princeton, N.J.
Product: MDX-010

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Clinical Status,
from previous page

Business: Cancer
Molecular target: CTLA-4 (CD152)
Description: Humanized monoclonal antibody against CTLA-4
Indication: Treat stage III or stage IV metastatic melanoma
Endpoint: Objective response rate; disease progression and survival
Status: Phase III started
Milestone: NA

MEDX began a U.S. Phase III trial in about 750 patients who will receive either MDX-010 in combination with MDX-1379, MDX-010 alone or MDX-1379 alone. This trial has an SPA *(see BioCentury Aug. 30)*. MDX-010 has Orphan Drug designation from FDA for this indication. MDX-1379 is a gp100 melanoma peptide vaccine

Product: MDX-066
Business: Infectious
Molecular target: C. difficile toxin A
Description: Human monoclonal antibody against C. difficile toxin A
Indication: Treat Clostridium difficile-associated diarrhea (CDAD)
Endpoint: NA
Status: Phase I start
Milestone: NA

MEDX will begin a dose-escalation Phase I trial in up to 30 healthy volunteers.

Metaphore Pharmaceuticals Inc., Fort Lee, N.J.
Product: M40403
Business: Neurology
Molecular target: Free radical
Description: Small molecule mimic of superoxide dismutase
Indication: Treat moderate to severe cancer pain
Endpoint: Safety, analgesic activity; pharmacokinetics
Status: Phase II started
Milestone: Phase II data (03/05)

Metaphore began a double-blind, placebo-controlled, U.S. Phase II trial in 24 patients.

NexMed Inc. (NEXM), Robbinsville, N.J.
Product: InnoNyx (NM100060)
Business: Infectious
Molecular target: NA
Description: Antifungal nail lacquer
Indication: Treat nail fungal infection (onychomycosis)
Endpoint: Safety and pharmacokinetics
Status: IND submitted
Milestone: NA

NEXM submitted an IND to begin a double-blind, U.S. Phase I study in about 75 patients.

Repligen Corp. (RGEN), Waltham, Mass.
Product: Secretin (RG1068)
Business: Neurology
Molecular target: Unknown
Description: Synthetic human secretin
Indication: Treat obsessive compulsive disorder (OCD)
Endpoint: Safety
Status: Phase I started
Milestone: Phase I data (year end 2005)

RGEN began an open-label, dose-escalation, U.S. Phase I trial in up to 16 patients who will receive subcutaneous RG1068 three times a week for one month.

Salmedix Inc., San Diego, Calif.
Product: SDX-101
Business: Cancer
Molecular target: Cyclooxygenases (COX)
Description: Single isomer R of etodolac
Indication: Treat chronic lymphocytic leukemia (CLL)
Endpoint: Response rate
Status: Phase II started
Milestone: NA

Salmedix began an open-label, international Phase II trial in 80 patients who will receive a standard chlorambucil regimen alone or in combination with SDX-101.

Product: SDX-102
Business: Cancer
Molecular target: NA
Description: L-alanosine inhibitor of adenylosuccinate synthetase
Indication: Treat brain cancer
Endpoint: Safety and tumor response; time to progression
Status: Phase I/II started
Milestone: NA

Salmedix began an open-label, U.S. Phase I/II trial.

Vical Inc. (VICL), San Diego, Calif.
Product: CMV trivalent vaccine
Business: Infectious
Molecular target: NA
Description: DNA vaccine encoding phosphoprotein 65, glycoprotein B and immediate early 1 (IE1) immunogen
Indication: Treat cytomegalovirus (CMV) infection
Endpoint: Safety; immunogenecity
Status: Phase I started
Milestone: Preliminary Phase I data (11/04)

VICL began an open-label, U.S. Phase I trial in up to 40 healthy subjects. Initial data are expected to be presented in November at the Interscience Conference on Antimicrobial Agents and Chemotherapy in Washington.

OTHER RESEARCH NEWS

BioAlliance Pharma S.A., Paris, France
Product: Styrylquinolines (SQs)
Use: Treat HIV infection

Researchers published in *Molecular Pharmacology* that SQs specifically and efficiently inhibit the nuclear import of HIV-1 integrase, thereby blocking viral replication of HIV-1 infected cells.

ID Biomedical Corp. (IDBE; TSE:IDB), Vancouver, B.C.
Product: Cell culture-based influenza vaccine
Use: Vaccinate against influenza

NIH awarded IDBE a $9.5 million grant to develop a cell culture-based influenza vaccine.

MacroPore Biosurgery Inc. (FSE:XMP), Frankfurt, Germany
Product: Adipose tissue-derived regenerative cells
Use: Treat myocardial infarction (MI)

In a swine model of MI, adipose tissue-derived regenerative cells improved heart function. Intracoronary infusion of these cells 48 hours after infarction was safe and significantly improved left ventricular ejection fraction (LVEF) compared to control as measured by 2-D echocardiography (p=0.01). Data were presented at the Transcatheter Cardiovascular Therapeutics Scientific Symposium in Washington.

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OFFERINGS & SECURITIES TRANSACTIONS

Week ended 10/1/04. Shares after offering refers to shares outstanding. Proceeds are gross, not net. Shares offered don't include overallotments. Currency rates used in the week: C$=US$0.7843; €=$1.2262; £=$1.8041

Completed Offerings

Arc Pharmaceuticals Inc., Vancouver, B.C.
Business: Drug delivery, Inflammation, Autoimmune
Date completed: 9/28/04
Type: Venture financing
Raised: C$1.6 million (US$1.3 million)

Arius Research Inc. (CDNX: ARI), Toronto, Ontario
Business: Cancer
Date completed: 9/28/04
Type: Private placement of common stock and warrants
Raised: C$2.6 million (US$2 million)
Shares: 3.4 million
Price: C$0.75
Shares after offering: 10.3 million
Investor: Biotechnology Value Fund
Note: The investor also received warrants to purchase an additional 3.4 million shares at C$0.75

Date completed: 9/28/04
Type: Private placement of convertible debentures and warrants
Raised: C$89,252 (US$70,000)
Investor: Loewem Ondaatie McCutcheon
Note: The convertible debentures bear 20% interest annually and convert at C$0.90. The investor also received warrants to purchase an additional 78,000 shares at C$0.90.

Cellective Therapeutics Inc., Durham, N.C.
Business: Antibodies
Date completed: 9/29/04
Type: Venture financing
Raised: $27.5 million
Investors: Intersouth Partners; Alta Partners; BA Venture Partners; Forward Ventures; Genentech Inc.; Latterell Venture Partners; MedImmune Inc.; Sofinnova Partners

Coley Pharmaceutical Group, Wellesley, Mass.
Business: Cancer, Infectious, Inflammation
Date completed: 9/28/04
Type: Venture financing
Raised: $25 million
Investors: Thomas, McNerney & Partners; Venrock Associates; TVM Techno Venture Management; Global Life Science Ventures

Human Genome Sciences Inc. (HGSI), Rockville, Md.
Business: Cancer, Infectious, Autoimmune
Date completed: 9/29/04
Type: Private placement of subordinated notes
Raised: $250 million
Shares after offering: 130.2 million
Overallotment: $50 million
Note: HGSI, which proposed to raise $200 million on Sept. 27, said it intends to use the proceeds to repurchase a portion of its outstanding convertible subordinated debt

Myogen Inc. (MYOG), Boulder, Colo.
Business: Cardiovascular
Date completed: 9/27/04
Type: Private placement of common stock and warrants
Raised: $60 million
Shares: 9.2 million
Price: $6.53

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Other Research News, *from previous page*

Osaka University Graduate School of Medicine, Osaka, Japan, et al.
Product: c-Jun N-terminal kinase (JNK) inhibitor
Use: Treat Type II diabetes

Researchers published in *Nature Medicine* that in a mouse model of Type II diabetes, a 10 mg/kg intraperitoneal injection of a JNK-inhibitory peptide significantly reduced blood glucose levels and insulin resistance compared to controls ($p<0.01$ and $p<0.05$, respectively).

PolyMedix Inc., Philadelphia, Penn.
Product: Antibiotic compounds
Use: Treat infections

Polymedix said that in a mouse model of soft tissue infection, 3 out of 9 small molecule mimetics of host defense proteins showed positive activity. The company has selected PMX-10066 as its lead clinical candidate.

Prokaria Ltd., Reykjavik, Iceland
Product: ThermoPhi DNA Polymerase
Use: DNA amplification

Prokaria said it identified a DNA polymerase that is thermostable with high natural strand displacement and proof-reading activity.

University of Ulsan, Ulsan, South Korea, et al.
Product: Anti-4-1BB monoclonal antibody
Use: Treat rheumatoid arthritis (RA)

Researchers published in *Nature Medicine* that anti-4-1BB antibodies inhibited disease onset in a mouse model of RA. The antibodies were shown to induce indolamine 2,3-dioxygenase (IDO), which is thought to suppress the CD4 T cells that are responsible for disease progression.

Wellcome Trust Sanger Institute, Hixton, U.K., et al.
Product: HER2 tyrosine kinase gene mutations
Use: Treat lung cancer

Researchers published in *Nature* the identification of mutations within the kinase domain of HER2 in 5 of 120 non-small cell lung cancer (NSCLC) tumors and 5 of 51 adenocarcinomas. The researchers suggest that Herceptin trastuzumab, a humanized antibody against HER2, could be used to treat lung cancer. Herceptin is marketed to treat metastatic breast cancer by partners Genentech Inc. (DNA, South San Francisco, Calif.) and Roche (SWX:ROCZ, Basel, Switzerland).

Completed Offerings,
from previous page

Shares after offering: 35.7 million
Placement agents: CIBC World Markets and Lazard Freres
Investors: New Enterprise Associates; InterWest Partners; Perseus-Soros BioPharmaceutical Fund; Sequel
Note: Investors also received warrants to purchase 1.8 million shares at $7.80

NicOx SA (NM:Nicox), Sophia Antipolis, France
Business: Neurology, Cardiovascular, Dermatology
Date completed: 9/30/04
Type: Private placement
Raised: €26 million ($31.8 million)
Shares: 9.4 million
Price: €2.75
Shares after offering: 32.1 million
Note: Nicox said a portion of the funds will be used to develop HCT 3012 to treat osteoarthritis (OA) and NCX 4016 to treat peripheral arterial disease (PAD)

Sciona Inc., Havant, U.K.
Business: Diagnostic
Date completed: 9/20/04
Type: Venture financing
Raised: $4.1 million
Investors: Burrill & Co.; Prelude Trust; BASF Venture Capital; DSM Venturing
Note: The nutritional genetics company hopes to raise an additional $1.9 million in a second closing this quarter

Sidec Technologies AB, Stockholm, Sweden
Business: Proteomics
Date completed: 9/13/04
Type: Venture financing
Raised: $5 million
Investors: FEI; Karolinska Investment Fund; Industrifonden; Karolinska Development

Solexa Ltd., Cambridge, U.K.
Business: Microarrays, Chemistry, Genomics
Date completed: 9/29/04
Type: Venture financing
Raised: $14.4 million
Investors: Amadeus Capital Partners; Abingworth Management; Schroder Ventures Life Sciences; Oxford Biosciences Partners

Vicuron Pharmaceuticals Inc. (MICU; NMerc:MICU), King of Prussia, Penn.
Business: Infectious
Date completed: 9/30/04
Type: Follow-on
Raised: $70.8 million
Shares: 4.8 million
Price: $14.75
Shares after offering: 59.6 million
Underwriter: Morgan Stanley
Overallotment: 720,000

Proposed Offerings

CardioVascular BioTherapeutics Inc. (Proposed:CVBT), Henderson, Nev.
Business: Cardiovascular
Date announced: 9/27/04
Type: IPO
To be raised: Up to $20 million
Shares: 2 million
Price: $10
Underwriter: First Dunbar Securities
Overallotment: 300,000

MediciNova Inc., San Diego, Calif.
Business: Chemistry, Proteomics
Date announced: 10/1/04
Type: IPO
To be raised: Up to $100 million
Shares: To be determined
Price: To be determined
Shares after offering: To be determined
Underwriter: Daiwa Securities
Overallotment: To be determined
Note: The company plans to list its shares on the Tokyo Stock Exchange's market of the high-growth and emerging stocks (MOTHERS)

VASTox plc, Oxford, U.K.
Business: Supply/Service, Genomics
Date announced: 9/30/04
Type: IPO
To be raised: £15 million ($27.1 million)
Underwriter: KBC Peel Hunt (advisor and broker)
Note: The chemical genomics company intends to list on London's AIM this month with a post-money valuation of £45 million

Other Financial News

Cubist Pharmaceuticals Inc. (CBST), Lexington, Mass.
Business: Infectious
Date announced: 9/29/04

CBST filed a shelf registration covering the sale of up to $100 million of stock. CBST, which closed Friday at $9.86, has 40.3 million shares outstanding.

Genentech Inc. (DNA), South San Francisco, Calif.
Business: Biopharmaceuticals
Date announced: 9/29/04

DNA's board increased the maximum number of authorized shares under its stock repurchase program to 50 million from 25 million, and increased to $2 billion from $1 billion the amount of stock the company can repurchase. As of Aug. 31, DNA has repurchased about $748 million of stock since the program began in December 2003. DNA had 1.1 billion shares outstanding as of Aug. 31.

Keryx Biopharmaceuticals Inc. (KERX; LSE:KRX), New York, N.Y.
Business: Renal, Cancer
Date announced: 9/29/04

KERX filed a shelf registration covering the sale of 5 million shares. KERX, which closed Friday at $11.18, has 30.7 million shares outstanding.

Nastech Pharmaceutical Co. Inc. (NSTK), Bothell, Wash.
Business: Drug delivery
Date announced: 9/30/04

NSTK filed a shelf registration covering the sale of up to $80 million of common shares, warrants and debt. NSTK, which closed Friday at $13.11, has 13.3 million shares outstanding.

S**witch Biotech AG**, Martinsried, Germany
Business: Dermatology, Functional genomics
Date announced: 9/21/04

The company filed for insolvency on Sept. 3. As a result, it will now focus on dermatology and divest non-core diabetic foot ulcer assets.

YM BioSciences Inc. (TSE:YM; LSE:YMBA), Mississauga, Ontario
Business: Cancer
Date announced: 9/30/04

The company began trading on AMEX on Oct. 1 under the symbol YMI. Its shares will continue to trade on the TSE under the symbol YM and on London's AIM under the symbol YMBA.