# 2003: What lessons for European biotechnology?

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## Abstract

The biotech sector had a sizzling year last year, raising US$19bn in cash globally. This paper looks at the performance of the biotechnology sector on both sides of the Atlantic in terms of financing activity. Financing activity in the European biotechnology industry is still a long way off from the USA, with public fundraising only reaching the level that the USA had in 1997 and venture capital financings getting close to the US levels of 1994–95. This suggests that at least another five to eight years is needed before there is even a chance to get near where the USA is today. However, the sheer size of the US equity capital market and its liberal attitude to fundraisings and higher-risk appetite is likely to mean that European biotechs will never catch up with the USA, even if our science (across the whole of Europe) is as good. This does not mean that Europe cannot have a thriving biotechnology industry. Indeed, the current level of activity in the venture capital and public markets suggests that Europe is only just getting serious on biotechnology.

***Keywords:*** *biotechnology, European, IPO, fundraising, licensing, Phase II*

## INTRODUCTION

Having started the first quarter of 2003 looking into the abyss, and contrary to most predictions, the biotechnology sector on both sides of the Atlantic posted a startling performance. March marked the turnaround point for the sector (and the market as a whole), ending the three-year-long decline of the markets. The performance of all the indices looks even more impressive if they are taken from this point in the cycle.

The Nasdaq Biotech index ended the year 42 per cent higher than where it began, putting the 22 per cent rise in the S&P500 to shame (Figure 1). The UK did not do too badly either, with the Nomura UK Lifesciences index up 32 per cent in 2003 versus 15 per cent for the FTSE AllShare index. However, given the extent to which Continental European biotechs had fallen, their return to favour was marked by a much bigger rise in 2003, clocking-up a huge 70 per cent gain.

So what helped dig the sector out of the rut? There were both sector-specific and non-specific events that may be put forward as catalysts for the stellar performance of biotechs. On the latter, the stock markets in general saw a revival of fortunes, with investor risk appetite coming back to the market – the main trigger being a quicker end to the (initial phase of the) Iraq war. The accommodative stance of the US and European central banks also fed huge amounts of liquidity into the financial markets. This was the main story in 2002–03. There then followed speculation about a resumption of


**Figure 1:** Performance of US and UK biotechnology sectors in 2003
Source: Datastream

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economic growth in the USA that has since been confirmed by a steady stream of supportive economic data.

There were also the biotechnology-specific events, which may have given a further boost to the sector. The following made the most significant contribution.

- More friendly Food and Drug Administration (FDA). The new FDA commissioner is seen as a more industry-friendly head. Some have attributed the surprise approval of Millennium Pharmaceuticals' Velcade in a record four months to this.
- Good clinical data. We owe a lot to both Avastin and Erbitux coming out with surprising data.
- Biotech earnings momentum continued, with many companies beating analyst forecasts by a significant margin and not just the usual 1 per cent.

**2003 was the year of the biotech convertible bond and the year the IPO window opened**

It would be good to think that biotechnology is where it is today because investors rediscovered their love for drug development companies, but the most significant driver was a rise in investor risk appetite. In other high-risk sectors, the performance of all but the European biotechnology index was dwarfed by that of the Nasdaq Technology index, which was up 62.8 per cent in 2003. The Nasdaq Computer index was up 43 per cent, a performance in line with the US and UK biotech indices. The take-home message is that, at least in this cycle, the overriding factor was a rise in investor risk appetite rather than any significant sector-specific event. Of course, if the developments in the sector had been negative, this performance would have been dampened, but there would still have been an up year. This view is not by any means intended to ignore the value generated by specific companies such as Genentech and Imclone in the USA, Alizyme and Pharmagene in the UK, and Actelion in Europe (this is not an exhaustive list).

## FUNDRAISING AND IPO ACTIVITY IN 2003

2003 will be remembered as the year of the biotechnology convertible bond, as well as the year that the biotechnology initial public offering (IPO) window re-opened.

### Fundraising by public companies

2003 turned out to be the best financing year for biotechnology after the sizzling performance in 2000, which holds the record for the best-ever year. Despite this, of the US$19bn (Table 1) that was raised in 2003, only US$0.5bn came from IPO activity, which was mainly focused on the last quarter of the year. As ever, the UK and continental Europe lagged significantly behind the USA but nevertheless put in a reasonable performance, managing to eke out £121.7m in the UK and $870m in the EU ($720m of which was Serono's convertible loan note in November) in combined private and public funding.

**Table 1:** Funds raised in biotechnology globally (US$bn)

| Year | VC | IPO | Secondary | Other | Total |
|---|---|---|---|---|---|
| 2003 | 3.655 | 0.506 | 3.796 | 11.091 | 19.048 |
| 2002 | 3.603 | 0.251 | 1.000 | 6.601 | 11.455 |
| 2001 | 4.343 | 0.408 | 4.050 | 7.412 | 16.213 |
| 2000 | 4.774 | 8.683 | 11.152 | 12.808 | 37.417 |
| 1999 | 1.801 | 0.963 | 1.452 | 3.635 | 7.851 |

Other includes convertible loan issues, debt and private investment in public equities (PIPES)
Source: Biocentury

Thus, according to calculations and at current exchange rates, UK and Europe managed a total of $1,089m in secondary issues.

In the order of US$7.0bn was raised in the form of convertible notes. Of these, the most notable convertible issues were those by Cephalon and Sepracor, given their 0 per cent coupons and having been issued at par. Cephalon raised US$750m in April 2003 (just as the biotechnology sector got going) by issuing a zero coupon 30 year loan. Similarly, in December 2003, Sepracor announced another zero-coupon note. The reason some biotechs, which are high beta and risky companies, could get away with such easy terms on their loan issues had more to do with the insatiable appetite for convertible loans than a specific interest in biotechnology loan notes. Nevertheless, these issues are now both in the money and, whether by design or luck, investors in these bonds have done very well.

**The proportion of start-ups vs refinancing was not that different from past years in the USA and UK**

## Venture capital (VC) financings

Looking at private fundraisings (VC-led only), the numbers on this side of the Atlantic were not too bad. Thus, US$886m was raised in private rounds in Europe and the UK compared with US$2.8bn in the USA. Only six out of 24, ie 25 per cent, of these were seed investments in completely new companies. Interestingly this is very similar to the USA, where 17 out of 73, ie 23.3 per cent, of investments went into start-ups. Contrary to common belief, the proportion of start-ups versus re-financings of already existing companies is not that different from the long-term averages of about 28 per cent.

**A number of IPOs have successfully priced in 2004 and some of those have gone to significant premiums**

## IPOs

IPOs trailed the opening of the secondary market window by about six months (Table 2). Of the companies that did IPOs in 2003–04, only one was in the UK, which has been trading above its issue price ever since float. Of the US IPOs, three were trading above their IPO price as of at the end of 2003. At the time, this led many investors to question the viability of the IPO window. However, although the data show that by 8th March, 2004, the situation had not changed, a number of IPOs have successfully priced in 2004 and some of these have gone to significant premiums. Consider the following lessons from the recent IPOs.

- It was often said that companies have to have a market cap of at least US$500m to get on investors' radar screens. The average market cap of the

**Table 2:** 2003–year to date 2004 IPOs

| Company | Activity | Amount raised ($m) | Market cap at issue ($m) | Issue price ($) | Price on 8th March ($) | Performance (%) | Date |
|---|---|---|---|---|---|---|---|
| Acusphere | Drug delivery | 52.5 | 199.8 | 14 | 8.55 | –39 | Oct. 03 |
| Advancis | Drug delivery | 60 | 226.9 | 10 | 8.74 | –13 | Oct. 03 |
| CancerVax | Cancer vaccines | 72 | 320.4 | 12 | 12.25 | 2 | Oct. 03 |
| Genitope | Cancer vaccine | 33.3 | 166.7 | 9 | 11.56 | 28 | Oct. 03 |
| Myogen | Cardiovascular | 70 | 359.2 | 14 | 15.6 | 11 | Oct. 03 |
| NitroMed | Cardiovascular | 66 | 279.4 | 11 | 8.72 | –21 | Nov. 03 |
| Pharmion | Specialty pharma | 84 | 334.6 | 14 | 22.6 | 61 | Nov. 03 |
| **Sinclaire (UK)** | **Specialty pharma** | **39.4** | **111.6** | **115p** | **149p** | **30** | **Dec. 03** |
| Eyetech | Ophthalmic | 136.5 | 808.5 | 21 | 35.3 | 68 | Jan. 04 |
| GTx | Men's health | 78.3 | 356.6 | 14.5 | 11.3 | –22 | Jan. 04 |
| Renovis | Neurological | 66 | 283.6 | 12 | 15.15 | 26 | Jan. 04 |
| Dynavax | Infectious disease | 45 | 177.6 | 7.5 | 8.3 | 11 | Feb. 04 |
| **Ark Therapeutics (UK)** | **Various** | **103.2** | **314** | **133p** | **138p** | **4** | **Feb. 04** |

Close of business 8th March, 2004. Companies in bold are from the UK
Source: Nomura Equity Research

2003 issues was US$302m.

- It was suggested that companies would have to raise at least US$100m for the IPO to be worthwhile. The average amount of cash raised has been US$69.7m.

**Reasons for poor IPO performance**

There are a number of possible reasons for why some of the IPOs have not gone well.

- As ever, the IPOs came at or near to the top of the cycle. The Nasdaq biotech went into a two month period of decline, having peaked on 23rd September, 2003, just as the IPOs were being priced.

**Comparison between the USA and Europe highlights the significant difference between the absolute level of activity in the two areas**

- It is difficult to see how fund managers were happy to buy IPOs in the last quarter of a year in which their funds had probably registered pretty good performances. Thus, it is likely that most investors were probably buying into the IPOs with the hope of seeing them go to a premium on the first day of trading. As the stocks began to fall below the issue price, the stop losses that were likely triggered would have exacerbated the share price falls.

- A number of the companies were probably not as high quality as one would have liked to see exiting at the opening of a nascent IPO window. Some of the players had been on their sixth or seventh VC rounds.

## The historical trends show that Europe is just getting started

Figure 2 summarises details of the financing activity in the biotechnology sector in the USA and Europe. Although they follow the same trend with a significant rise in the level of funds raised in the 2000–03 period, the comparison between the USA and Europe does highlight the significant difference between the absolute level of activity in the two areas. Thus, excluding 2000, the level of public financing activity in Europe has only just risen above that of the USA in 1994. On the private side, the activity level is now at about the level reached by the USA in 1997. Thus, on these measures European biotechnology is five to eight years behind the USA. Indeed, comparing the quality of public European biotechnology with the USA, a favourite pastime of European fund managers, biotechnology executives and the media, is futile as the public companies of today are the result of VC investments in 1994–95 which in Europe totalled US$54m for the two years combined.

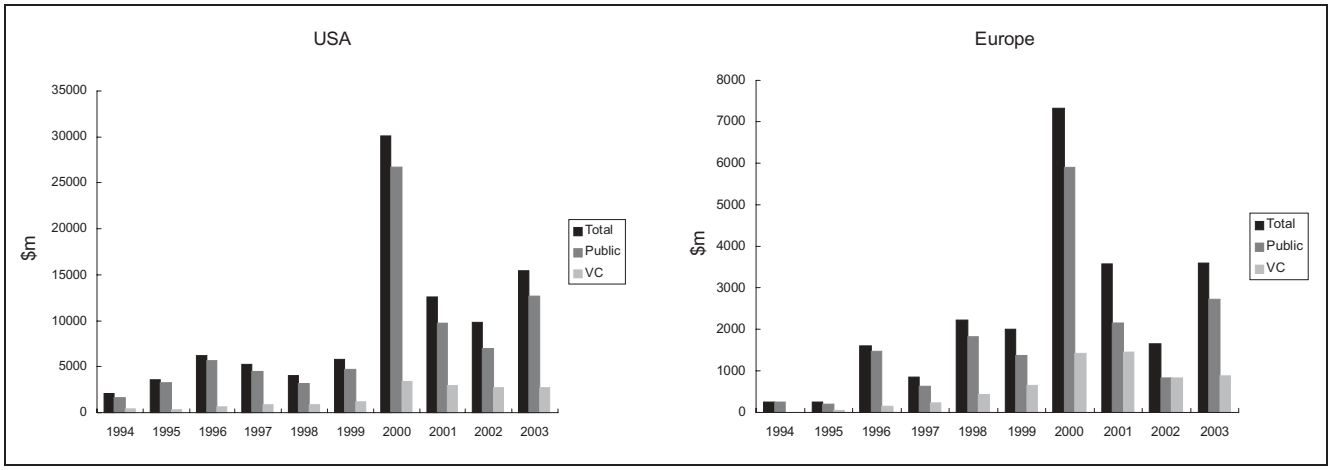


**Figure 2:** History of US and European fund raisings
Source: Nomura Equity Research

**Analysis suggests that the European biotechnology industry is just getting going**

Analysis suggests that the European biotechnology industry is just getting going. This is also supported by the number of mature private companies in VC portfolios, and the increased level of financing that these are attracting. Examples include the UK's Lorantis, Arrow and Kudos which attracted US$41.8m, US$35.3m and US$45m in recent financings, respectively.

At current financing levels, Europe will never catch up with the USA. However, this should not be expected to be the case, as the equity markets of the countries that currently account for most of the biotechnology activity in Europe (ie UK, France, Germany and Switzerland) have a total market capitalisation that is barely 40 per cent that of the US stock markets, which is currently valued at just above US$11trn. It is a wonder that there are still a number of success stories, including Acambis, Serono, Actelion, Celltech and Qiagen. Thus, the sheer size of the US equity capital markets, their liberal attitude to fundraisings and higher-risk appetite is likely to mean that European biotechs will never catch up with the USA, even if our science (across the whole of Europe) is as good.

**The sheer size of the US equity capital markets, their liberal attitude to fundraisings and higher-risk appetite is likely to mean that European biotechs will never catch up with the USA**

## PHASE II DATA ARE SWEET FOR BIOTECHNOLOGY

The big news in the UK was positive Phase II data on two of Alizyme's products which have now positioned Alizyme as one of the potential winners in the UK biotechnology industry. Alizyme started 2003 with a share price of 33p and ended the year at 171p, a performance of 518 per cent. The general rise in the stock market and the biotechnology sector probably accounted for 10 per cent of this rise; the rest of it, in the author's view, was due to the successful completion of three Phase II trials, one on the company's obesity drug and two on its treatment for irritable bowel syndrome. The markets response supports the view that Phase II data are a significant value inflection point for biotechnology companies.

**Good Phase II data from a properly conducted trial could be the most valuable asset a biotech company has**

Further evidence in support of this view came from the recent deal between Pfizer and Esperion. Pfizer announced on 22nd December, 2003, its plans to acquire Esperion Therapeutics for $1.3bn in cash. This was a 54 per cent premium to Esperion's average closing share price over the previous 20 trading days. Pfizer believed that Esperion's cardiovascular therapeutics would add a significant string to its own cardiovascular franchise's bow, which is based on lipid-lowering drugs. The history of this company and its lead drug is a very interesting and circular one.

Esperion recently published Phase II clinical results for ETC-216 to treat acute coronary syndromes (ACS). The data showed that the compound met the primary end-point of reducing fatty plaque volume compared with baseline. ETC-216 increases high-density lipoprotein (HDL; good) cholesterol, while Lipitor, Pfizer's blockbuster cholesterol drug, lowers low-density lipoprotein (LDL; bad) cholesterol. Pfizer already had US co-marketing rights to ETC-216 and an option to take ex-North American rights. The trigger for Pfizer to take Esperion out was probably that the net present value (NPV) of the royalties the company would have had to pay to Esperion was probably higher than the cost of buying the company.

This deal provides a number of lessons, the most significant of which is that good Phase II data from a properly conducted trial could well be the most valuable asset that a biotechnology company has.

In conclusion, biotechnology companies should retain rights to their products until after the end of Phase II trials and should not skimp on conducting the right Phase II trial programme. Investors need to support this.

## 2004 SECTOR OUTLOOK

So what does 2004 have in store? The general market will be looking for continued evidence of the economic revival in the USA, with anticipation that this will be reflected in the profits of US companies in the first quarter. Profit

**Profit growth appears almost certain given the low base with which it will be compared**

**Impact on job creation**

growth appears almost certain given the low base with which it will be compared. The issue is probably the extent of the growth. The questions that will probably exercise investors' minds will then be the sustainability of the profits revival going into the second half of 2004 and 2005, and how much of it will feed through to job creation. Whatever the case, although the bullish mood in the market is expected to continue and contribute to stock performance, in 2004 the biotechnology sector will have three issues to deal with.

**Important issues for 2004**

- It is likely that generalist investors will be looking to rotate out of high-risk stocks into more cyclical stories to capture the full impact of the profits revival.

- With the liquidity-driven part of the cycle reaching its climax, the next phase will require greater discernment. Investors can no longer just buy any biotechnology company and expect the stock to rise on the back of a rising risk appetite and better sentiment toward the industry (as they could have done in 2003).

- If the current prediction of a general market downturn in the second half of 2004 driven by a turn in the interest rate cycle and a significant slowdown in consumer spending is correct, then a relatively more painful downturn in the biotechnology sector is predicted, given its high beta.

**Only when a few more European biotechs have made it into the big league will the pressure abate**

Thus, the investment thesis for 2004 is one of stock picking in the first half and some profit taking before going into the summer lull in case a downturn does come in the second half.

## Biotechnology cash needs in 2004

In 2004, public companies will continue to attract the bulk of investment interest from institutions. IPOs will remain few and far between. Fundraisings in the US biotechnology sector will continue apace. There is a good chance that the USA will continue with its slow run of biotechnology IPOs and these will, at least initially, put in a better performance than the ones seen so far. This is because the general quality of the companies looking to exit is better (based on companies that have recently filed with the Securities and Exchange Commission [SEC]) and that valuation expectations are likely to be tempered by the performance of the recent issues (see Table 2).

## Fundraising by UK public companies

There is sufficient investor appetite in the UK and Europe to continue the reasonably successful run of fundraisings by public companies seen in the last quarter of 2003 (four companies raised a total of £69.8m in the UK). However, it must be realised that the European fund manager has had much more experience of disasters than positive company developments. This is all the more problematic as there is a constant comparison with the USA, where the sector is more mature and generally believed to be more successful. This was not a problem for US companies as investors who bought into early US biotechs had nothing to compare those companies with and as such were investing in companies based on their absolute and not relative remits. There is sadly no rapid solution to this problem. Only once a few more European biotechs have made it into the big league, which should be in the next five years, will the pressure abate.

Table 3 summarises the estimated cash-life of some UK companies, and clearly shows that few actually seem to have a significant need to raise money. Thus, fund managers will not find it necessary to keep their powder dry for investments in their portfolio companies as very few of these are desperate for cash. Furthermore, the cash that has been returned by UK companies that have been acquired recently (in particular Intercare and

**Table 3:** Cash needs of companies covered in this paper

| Company | Nomura's cash estimate | Nomura estimate of cash life, 1st January, 2004 | Comment |
|---|---|---|---|
| Acambis | Dec. 2003: £118.6m | >3 years | |
| Alizyme | Dec. 2003: £21.9m | Early 2006 | |
| Antisoma | June 2004: £32.0m | >3 years | If R1549 fails then mid-2006 |
| Biocompatibles | Dec. 2003: £48.8m | >3 years | Cash estimate excludes escrow of £17.6m |
| CAT | Sept. 2004: £78.9m | Mid-2006 | |
| Celltech | Dec. 2003: £123.4m | – | Celltech is a cash-generative business |
| Galen | Dec. 2003: −£245.5m | – | Galen is highly cash generative and is paying down its debt |
| Medisys | – | – | Company is self-financing, but has net debt |
| Pharmagene | Dec. 2003: £16.0m | Late 2005 | Pharmagene should raise money to invest more in its products |
| Phytopharm | Aug. 2004: £10.3m | Late 2006 | Estimates assume that Yamanouchi milestones will be received mostly in 2004 |
| Profile Therapeutics | June 2004: −£0.38 | Mid-2004 | Company has £5m debt facility that it can use |
| Shire Pharmaceuticals | Dec. 2003: £1028.9m | – | |
| Vernalis | Dec. 2003: £28.0m | Mid-2005 | This forecast assumes no further payments from Elan |
| Xenova | Dec. 2003: £5.0m | Mid-2006 | Company raised around £21m in December which comes into our model in Jan. 2004 |
| XTLbio | Dec. 2003: $21.5m | Mid-2005 | |

These figures do not include any upfront or milestone income from deals that have yet to be signed
Source: Nomura Equity Research

possibly Amersham) will probably be looking for a home in the UK sector. As a result, there will be funds available for investment in companies that are tapping the market for two reasons:

- a sensible change in business strategy; and/or
- to invest in successful products.

Indeed, some evidence of this has already been seen from the fundraisings of 2003. On the back of a run of very good news on its products, Alizyme raised £11.4m to allow it to begin further clinical trials on some of these products so as not to lose valuable time (and hence future potential sales) while it is looking for a partner. Antisoma raised £15.2m to fund expanded clinical development plans for some of the products already in its pipeline.

## IPOs in Europe?

**Has the IPO window opened in Europe?**

There is much debate about whether the IPO window will open in the UK (and Europe). The successful flotation of Sinclaire Pharma and Ark Therapeutics signal that this may have already happened. However, Sinclaire is a profitable specialty pharmaceutical company and is, in the author's view, about as 'biotech' as a bakery business. Ark Therapeutics has a product on the market and a number of other products in Phase II and Phase III. The real question is whether there will be any appetite for an IPO where the bulk of the money will be going toward the development of clinical stage products in a company that will not have any marketed products for a number of years to come (ie a classic biotech story). Companies would need to pass a number of tests that are seen as important contributors to attracting investor attention, and hopefully cash, in the UK.

- Positive Phase II data on at least one product (based on generally accepted end points and not unproven surrogate markers). This is one of the most important issues. Until a company has produced meaningful efficacy data in humans, then the risks are far too high for generalist investors. Phase II trials are the first time an interesting biological phenomenon is put to the test in a real

**In the current phase of the equity market, the risks of converting a biological phenomenon into a product should be taken by VCs**

patient setting. In the current phase of the equity market (unlike the late 1990s), the risks of converting a biological phenomenon into a product should be taken by VCs. What are good Phase II data? Placebo-controlled randomised trials in a large enough patient population which provides sufficient data to make the expensive decision of investing in Phase III trials and possibly attract a partner. Data from ten patients compared with historical data based on biomarkers that the company has invented are not enough.

- Strong management teams with proven track records. This is a very difficult area. Companies with management of enormous pharmaceutical experience go to the wall. The key is whether the management team has the right experience for the job. A great case to illustrate this is Esperion. This is a cardiovascular company working on treating cholesterol disorders. The company's management (founders) were the same team that discovered and developed Lipitor, Pfizer's blockbuster cholesterol-lowering agent. The company successfully developed a new product through to Phase II trials and is currently being acquired by Pfizer.

- A solid scientific and technology base from which the company can demonstrate the ability to continuously generate new product leads. Of course, this is not a significant issue for companies whose business models are based on an in-licensing strategy.

- A broad product pipeline. Clearly, biotechnology companies that have had a maximum of £20m–50m ploughed into them by VCs should not be expected to have four products in Phase II with one about to enter Phase III. But it is not too much to expect to see at least one completed Phase II trial with two or three products in Phase I and II behind it.

Companies looking to exit and investors buying these IPOs should realise, however, that if the prediction of a second-half downturn by some equity strategists turns out to be correct, then they may hit a period of considerable turbulence.