Presentation by William J. Kridel, Jr, on

"An Overview of Biotechnology in a European Context - and the Role of Corporate Partnering in Developing It"

Ladies and Gentlemen, Members of the Foundation for Strategic Research, Members of the Swedish Royal Academy of Sciences, Members of the Swedish Royal Academy of Engineering Sciences, Members of the Nobel Foundation, Distinguished and Learned Scientists from the World of Biotechnology, Honoured Guests, and Representatives of the Press:

As the representative of the Business and Finance communities and as counterpoint to all the eminent scientists preceding and following me, I am pleased to be able to address this diverse audience on the subject of "Biotechnology in Europe and the role of Corporate Partnering". I will initially give a brief overview of the European context, and then identify certain key factors which should be present to enable national success in the rapidly changing biotechnology industry. I will then finish with some illustrative guidelines on how smaller companies link up with larger pharmaceutical or biotechnology entities, a process known as "Corporate Partnering", a key determinant of company success.

The European biotechnology scene has really developed over the last ten to twelve years beyond its regional origins in the UK.....almost every country in Western and Central Europe now boasting at least one, if not dozens of, small and medium enterprises set up by scientists and engineers to create therapies, devices and processes which hopefully will come up with solutions to unmet medical needs. I will be drawing heavily upon the excellent annual biostatistical survey by Ernst & Young, and my own first hand business experiences, in painting a picture of the present European biotech field.

I. OVERVIEW OF THE EUROPEAN BIOTECH INDUSTRY

In 1997, there were over 1,000 European biotech companies, of which 60 were public, these numbers not including the larger, more visible pharma companies with a heavy biotech content such as Astra, Zeneca, Schering, Rhone-Poulenc and Novartis. Biotech life is burgeoning: the total population of Euro-biotech companies grew by 45% between 1996 and 1997, with an almost parallel increase in the number of employees rising from 27,500 to over 39,000. Sweden had approximately 90 such companies, whilst France had about 130 and Germany 170 and the UK almost 250. Most of these companies are very early stage and do not yet have significant sales revenues; although there are cash inflows to them from investors and from collaborators paying for interim technology access and for scientific/regulatory accomplishments prior to product launch.

The total revenues of the 1,000 plus Euro-biotech companies amounted to ECU 2.7B in 1997, compared to their US counterparts with ECU 16B for 1300 companies: these statistics show an average of ECU 2.7m per Euro-biotech company in revenue compared to ECU 12.3m for the average American biotech company. The implication? Not only do US biotechs have a larger scale to attract collaborators and investors, but also a larger operating mass from which prosperous survival can be managed. Also, due to the greater relative maturity of the US biotech industry, there are more companies there that have reached the stage of commercial revenues, and in some case even profits, whereas in Europe the revenues that have been achieved are almost all derived purely from technology access fees or milestones paid by Pharma collaborators, rather than from product sales.

The overwhelming majority of these European companies is fairly small, with less than 150 employees. It will come as no surprise to this body that these young, aggressive organisations emphasise classic activities like platform technologies, contract R&D, therapeutics and diagnostics. The raison d'être of the biotech industry is innovation and its lifeblood is R&D, with ECU 1.9B spent in 1997 by Euro-biotechs (up from ECU 1.5B the prior year), and the pace is certainly picking up, as all biotechs rush to fill the pipelines of Big and Medium Pharma, which groups in turn need to launch many New Chemical Entities (new drugs) per year to meet investor or family expectations for profits and sales growth.

Who are some of the leading biotech companies in Europe? Vanguard Medica and Cambridge Antibody in the UK, Innogenetics from Belgium, Genset from France, NeuroSearch from Denmark, Biora and KaroBio from Sweden.....all of whom have gone public in the last two years. There are scores of still-private companies developing their technology and/or preparing to launch products such as IDM from France in cancer vaccines, MediGene from Germany in gene therapy, Prolifix from the UK in controlling the cell cycle with small molecule drugs, and Eurona from Sweden in the revolutionary field of pharmacogenomics.

Almost all of the public and private companies were started by technically-oriented businessmen and scientists, with funding from venture capitalists. There is vast amount of venture capital from local/national sources such as Abingworth in the UK, TVM in Germany, Sofinnova in France, Viking Medical in Norway and Odlander Fredrikson & Co. from Sweden…….. as well as some pan-European investors like Atlas Venture, the Rothschild Bioscience funds and Lombard-Odier Immunology Fund. It has been estimated that over ECU 400m was provided by Venture Capitalists to Euro-biotechs in 1997, with recipients ranging from the UK to France to Denmark to Sweden (such as Eurona in December 1997) to Germany.....These monies were made available at all stages of corporate life, from pure R&D through to launched products, though the natural risk aversion of investors often lead them to prefer biotechs at least with later-stage clinical trials. Some Venture Capitalists specialise in very early stage investments, known as "seed" investments, and even participate in the very creation of new biotech companies: The Merlin Fund in the UK, the Medical Research Council Fund in the UK, Capricorn Ventures in the Netherlands, and Warburg Pincus, the US Venture Capital firm from its largely autonomous London office.

Of course, these venture investors would not take the risk of financing fledgling companies if there were not substantial rewards in view, normally from a quotation of their investee company on a national stock exchange (such as the German Neuer Markt or AIM in the UK) or EASDAQ for a Euro-listing, in an exercise known as an IPO (Initial Public Offering)..... In 1997, there were a number of excellent European IPOs and of the 12 largest ones, Sweden accounted for two, the UK six, France three and an American spin-off for one. Once quoted, all biotech companies experience the vicissitudes of real life wherein public market investors reward and punish that company based on its performance. The word "performance", though, has several meanings: (i) establishment of business collaborations; (ii) accomplishment of interim scientific goals (generally of a pre-clinical nature proving an important experimental hypothesis); (iii) achievement of regulatory milestones involving the filing for, and receipt of, permissions from Government authorities to go to ever more complex and larger trials in human beings; (iv) launch of therapeutic or diagnostic products; and eventually (v) hitting forecast sales targets in domestic and foreign markets. Needless to say, the performance of quoted biotech companies has been pretty volatile, sometimes based on their own disappointing results (frequently due, however, to over-inflated expectations), but often for no other reasons than a lack of arresting or headline news…….or bad news from a comparable company (in a phenomenon known as "sector disenchantment").

It is obvious that European biotech companies can seek permission from domestic and foreign regulatory bodies for their various clinical trials and product launches. Interestingly, they also have access to a supra-national body called the European Medicines Evaluation Agency which was created by the EU in an effort to harmonise rather disparate, costly and time consuming national regulatory regimes. In 1997, 22 products were approved by the EMEA, of which 11 can be classified as biotech. Strangely enough, none of those biotech products came from the small, adventurous biotech firms; rather they came from larger established companies like Hoechst, Lilly, SmithKline, Genzyme and Biogen. Is there a lesson in these approval statistics? Yes, the Euro-biotech company's day of fulfillment is drawing near, but has not yet arrived.

One of the factors that could accelerate the success of Euro Biotech is Corporate Partnering. Drawing from statistics prepared by Windhover's Strategic Intelligence Systems on deals concluded from 1991 to the present, we can note that Euro Pharma (of all sizes) greatly prefers transactions with American Biotech (457 deals with US Biotech companies versus 67 with Euro Biotech companies) and this attitude is mirrored somewhat by the behaviour of European Biotechs who have done 74 deals in this period with US Pharma companies versus 67 with Euro Pharma.

Just before we leave this rapid Grand Tour of Europe on Biotech, the Swedish audience should note that Astra and Pharmacia & Upjohn rank in the Top 20 pharmaceutical companies in the world in terms of sales and drugs under development (from their own R&D resources and from dozens of collaborations with smaller biotech innovators or academic institutions). Empirically, it can be seen from their Corporate Partnering experience that the role of small biotech companies clearly involves the supply of innovative products and technologies to their larger brethren.

II. INGREDIENTS FOR SUCCESS IN EURO- BIOTECHNOLOGY

At this point, the audience may well be asking itself "Just what are the key ingredients that must be mixed together to produce national success in the highly competitive and risky biotechnology field?" I shall segregate them into three categories: business, government and social.

Business Factors

Substantial and unfulfilled market opportunity on a scale large enough to motivate the creation of an enterprise in the first place

Access to plentiful private equity capital, primarily from venture capitalists and hopefully starting at a very early stage and continuing through to the IPO

Multiple sources of professional advice on technical, financial, strategic, clinical, and commercial topics.

Unique and patentable intellectual property that can lead to a sustainable competitive advantage.....and to early launch of products

Access to public equity financing from the local stock market and/or from compatible foreign stock markets, such as the NASDAQ in the US and EASDAQ in Europe, for the IPO and later financings

A determined and focused business plan for the enterprise which avoids excessive diversity of activity and diffusion of effort

Government Factors

Creation of a clear, speedy and unequivocal regulatory environment for medical devices, drugs and other therapeutics, as well as for diagnostics

Provision of swift and robust patent protection for innovators

Establishment of "orphan drug" regulations to encourage work in minimalist diseases

Financing in the form of low cost loans, grants and equity capital for start-up, and existing, enterprises to create and maintain momentum

Taxation policies for companies that recognise the capital-intensive and risk-laden nature of the biotechnology field: mainly special allowances for capital expenditure, R&D and continuing education plus low rates on corporate income when eventually earned

Taxation policies for individuals that encourage them (a) to invest in these high-risk enterprises by lowering or abolishing capital gains taxes, and (b) to work in such organisations by treating stock options and warrants favourably

Social Factors

Business schools that produce well-rounded, risk-aware, but entrepreneurial individuals

Science and Engineering schools to provide the training and intellectual capital

on which innovation is founded

The Press acting in a constructive fashion to create a social climate in which praise and encouragement of these science-business partnerships is prevalent - and where scare-merging or ill-informed speculation is avoided

Technology transfer mechanisms permitting the movement of knowledge, invention and even people from academia to the private sector

As I look around me, I notice that almost all of these pre-requisites for success are present in modern day Sweden and you can only be praised for understanding what was necessary. But all is not yet Paradise for Swedish Biotech! and I am sure that the collective deliberations of these assembled institutions will improve the existing Swedish context further.

It is important to note that other, late starting countries, in the race to develop a flourishing biotech industry, have created comprehensive programs, the best known of which is BioRegio in Germany (which along with changes in taxes and public opinion) has greatly accelerated the development of local biotechnology companies. The Southern Sweden and Eastern Denmark region, jointly known as Medicon, has made notable progress in the same way but since it spans two countries, is not as easily susceptible to such promotional efforts.

III. SOME THOUGHTS ON CORPORATE PARTNERING

Finally, it is important to understand the basics of Corporate Partnering, since this process is the primary industrial link between the small, innovative biotech company and its most frequent counterparty, the large pharmaceutical company. Moreover, Corporate Partnering and the ability to do it at all and then to do it well is both a reflection of, and consequence of, the above national success factors impinging on individual companies.

A. WHAT IS CORPORATE PARTNERING?

First, let's decide what it is not:

a simple licensing agreement
a simple marketing/promotion arrangement
an outright acquisition

Second, it might be in a joint venture, if a separate company format is used.

Third, it really is a giant club sandwich with many layers of financial flows transferred in exchange for technology and commercial rights:

license/technology access fee
R&D support funding
milestone payments
royalties

perhaps with the extra, piquant flavouring of equity investment.

B. WHY PURSUE A CORPORATE PARTNERSHIP?

There are two distinct sets of motivations which impact on the analysis and negotiation of a Corporate Partnering deal:

Biotech Company	Pharmaceutical Company Partner
Get cash in	Buy R&D at less costly price than in-house work to fill a product gap
Access to: . markets-foreign/US . clindev expertise . manufacturing base	Use existing, costly infrastructure in sales/marketing and regulatory/clinical affairs
Validation of technology to private investors or public stock markets	Access to innovation in technology or products
(All done without necessarily selling more equity)	(All done without an acquisition of an outside company)

There are thus combined practical and financial reasons for both sides to create a Corporate Partnership……with well-balanced and mutual incentives: the Biotech to survive and then prosper, and the Pharma to remain profitable and competitive.

In fact, I cannot say it any better than my friend Klaus Ebert (Head of Scientific Support Group, Boehringer Ingelheim) in an Ernst & Young interview:

> "No company, not even the biggest, can be technologically self-sufficient. Our biotech alliances expand and complement our in-house efforts to create a competitive technology basis for the next decade."

C. WHO PARTNERS?

The easy answer is everybody and the Corporate Partnering world is totally promiscuous in this hazy world of intimate relationships; but there are fewer and fewer Big Pharma and Medium Pharma counterparties because industry consolidation continues apace (most recently with Roche agreeing to acquire Boehringer Mannheim). Amongst Euro Pharmas, it is well known that, overall, UK and Swiss pharmaceutical companies are more active in deal-doing, although Germans, French, Scandinavians and Dutch are also playing the game….with occasional participation by Italians, Spanish and Irish.

D. WHEN IS CORPORATE PARTNERING DONE?

The contention that innovation, in the form of discovery R&D, is indeed linked by the Corporate Partnering process to the Pharma and Biotech counterparty is supported by statistics generated by Windhover: There were 536 such transactions in 1997, of which 51% took place at an early stage, that is at the R&D phase. American partners predominated over European significantly. Why this leaning by US Biotech and Pharma toward early-stage partnerships? Perhaps because Americans are less risk-averse, perhaps because the partnering enterprise is larger and therefore can afford to build a broad spectrum portfolio, perhaps because of a stronger desire to get the innovation benefits for themselves and keep them away from competitors. In any event, the message to the small, innovative Biotech company is positive: There are indeed many willing partners to back you, even at the discovery stage.

There is no hard and fast rule, but in general it can be said that:

The Biotech Company usually wants to partner at proof-of-principle (still pre-clinical) or Phase I, whereas

the Euro Pharma wants proof-of-efficacy as shown in Phase II, not just *in vitro* biological activity (pre-clinical research) plus safety (Phase I).

But Two Big Exceptions:

Unique, <u>therapeutic</u> platform technology (like the mesenchymal stem cell technology of Osiris) which addresses big markets; and

platform <u>discovery</u> or lead optimisation technology (like pharmacogenomics from Eurona here in Sweden).

E. HOW IS CORPORATE PARTNERING DONE?

by scientists, who know each other in a given field
by the corporate development/business development team at the Biotech company seeking a partner, <u>and</u> also by their counterparties in Euro or US Pharma seeking to fill in gaps in product, technology, or marketing
by outside advisors like my firm (Ferghana Partners) who are aware of the growth strategies of Big Pharma, Medium Pharma and Big Biotech in the USA, Europe and Japan.

II. HOW TO PICK A CORPORATE PARTNER (AND LEARN TO LOVE, AND LIVE WITH, THEIR IDIOSYNCRASIES)

There are four main ingredients to be considered in the choice of a corporate partner:

A. Therapeutic Fit
B. Corporate Style
C. Geographic Focus
D. Money

A. THERAPEUTIC OR TECHNOLOGY FIT - This term means how well the product or technology (a compound addressing a primary indication) fits into a Big Pharmaceutical company's portfolio; for example, "product fit" considerations would include:

by indication (like asthma)
by mechanism of action (like inhibition of the complement cascade in the immune system)
by sales force/target audience (like specialists, general practitioners, or hospitals)
by therapeutic category (like oncology)
by availability (such as Phase III or approved but not yet launched)

The Biotech company's perception of Therapeutic FIT must be clear and complete, so that an effective presentation of the business opportunity can be made to the Pharma counterparty - it is no use arguing with an opthalmology company to take on a respiratory compound. The fit will be much better if Discovery Compound X or Technology Y, or Marketable Drug Z actually fills a hole in the potential pharma partner's portfolio.

B. CORPORATE STYLE - This term has a purposefully vague aura….intended to convey both the internal characteristics of a possible Partner company and the external roles that it can play:

INTERNAL STYLE ELEMENTS

who makes decisions (on R&D, marketing etc.)?
is the partner company science-based (like Schering or Ares Serono) or marketing-driven (like Roberts Pharmaceutical or Medeva)?
how open is the Corporate Partner's culture to new ideas or is it "NIH" still
who is the internal "champion" of the Pharma Company to do a corporate partnering deal and what is his/her standing (i.e. power base)
how "easy" are the inter-personal relationships of scientists and business people at the Pharma Company amongst themselves and with an outside Biotech Company

A Biotech company may have many possible and willing partners, but the type of Pharma company chosen can affect whether or not the alliance will be successful.

EXTERNAL ROLE/STYLE

What does the Biotech Company want (or need) the Corporate Partner to do? (here is a partial checklist)

supply only money
add pre-clinical (animal modelling, PK, PD, tox) expertise
add clinical development trials experience
do the regulatory filings
manufacture the product
sell the product

The selection of external roles supplied to the Corporate Partner for it to play may affect the choice of Partner, as some Partners do not have all these skills available.

C. GEOGRAPHIC FOCUS - In general, every Pharma will want to cover at least all its local or regional market (and some nearby export markets)….with a Big Euro Pharma going for a global role/rights including the USA and a Medium Euro Pharma contenting itself generally with Europe but not the US.

D. MONEY - Not all Pharmas were born equally rich nor certainly have they all grown up with an identical dowry with which to tempt the Biotech bride. Is it obvious that the bigger the Partner's existing cash hoard and the annual cash flow, the better? Maybe…….but not-so-obviously it really depends on:

how badly the Pharma wants the Biotech company's product/technology for itself or to stop a competitor from getting it

how rigidly committed are the cash resources for prior internal or collaborative R&D efforts

how much cash the Biotech is aiming to extract for your company in a deal, relative to the Pharma's cash resources.

how much will the total deal cost (remember that the Corporate Partner often will also be paying all the clinical development and regulatory filing costs).

In general, global deals carry the highest price tags. These are the province of the US multinationals, but there are also Big Euro Pharmas left playing in this rarefied league:

Benelux	France	Germany	Switzerland
Akzo	RP	Boehringer Ingelheim	Roche
	Sanofi	BASF	Novartis
Scandinavia	UK	Bayer	Ares Serono
Astra	SKB	HMR	
P&U	Glaxo Zeneca	Schering	

III. WHAT ARE THE KEY CORPORATE PARTNERING ITEMS TO NEGOTIATE?

A. FIELD-OF-USE FOR THE PRODUCT/TECHNOLOGY

The Pharma counterparty will try to define it widely, but the Biotech company should tie it tightly to a single indication or to related indications or to a therapeutic field (each scalar increment at an escalating price, of course).

B. TERRITORY

The Biotech company should always ask a prospective partner to state, frankly, in which countries it has really strong operations and, by the same token, where it has little or no representation.

C. LICENSE FEES/TECHNOLOGY ACCESS FEES

This deal element, coming as it does upfront, often crystallises the inherent differences of motivation: the Biotech wants a Big Number to show off to investors, outside research collaborators and its own people…..while the Corporate Partner wants a Small Number to minimise its risk (till the product or technology proves itself more persuasively). The Biotech should attempt to argue that this fee represents the partial cost recovery of "the past and very valuable" R&D expenditures and that the money is needed to replenish its corporate/R&D coffers so as to remain "ahead of the curve" - and of course should come to the discussions armed with supportive evidence of similar deals that have recently been done.

D. R&D SUPPORT PAYMENTS

A careful analysis of the Biotech's research project-related costs (fully burdened with lab, materials, salaries etc) expressed as $/FTE, will need to be fully and openly presented to the Corporate Partner.

E. MILESTONES

These essentially constitute a series of rewards, to the Biotech, for its scientific, clinical or regulatory achievements. A recent rule of thumb has it that that total milestones "should be" 20% of the NPV of the first five years of the forecast royalty stream.

F. EQUITY LINKAGE

Some Pharma companies feel that their Corporate Partnering transaction with a Biotech provides a long term benefit to its shareholders in the form of a significant capital value uplift…and thus also may wish to benefit, by owning shares purchased as part of the Corporate Partnering deal (and prior to market recognition of the Biotech's thereby improved circumstances).

From the Biotech's point of view, the pricing of an initial equity stake by a Corporate Partnering is ideally at a 30-50% premium to the last private financing round (or in the case of a public company, to the recent market price) so as to give a constant upward impetus to the Biotech company's valuation.

G. ROYALTIES

These payments, designed to reward commercial success (i.e. sales), are so diverse in structure I will not attempt to list all the various permutations but here are a few:

fixed % vs scalar %
scalar % by tranche vs scalar % rolled back to first dollar
time adjusted\periodic vs cumulative
uniform across the world vs differentiated by region or country

Let me just say that as a rule, when the proposed upfront payments are modest (which is the usual preference of Big Pharma), it should be possible

to negotiate a more generous royalty payment. Royalty payments range from a few percentage points of revenues up to 30% or even higher. The highest royalty rates, all other things being equal, attach to the most unique products or proprietary technologies. In reality, those Biotechs that lean most heavily on the Big Pharmas for funding, clinical trials and manufacturing as well as marketing, will end up paying for this support by receiving modest royalties.

SUMMARY: It is beyond the scope of this talk to go into all the many "tricks of the trade" that enter into the successful negotiation of Corporate Partnering deals. Let me just say that the lands of Corporate Partnering are always changing in topography and no transaction is the same; thus, a firm like Ferghana Partners exists precisely to guide US and European Biotech companies through this mysterious territory to the happy and safe destination.

Ferghana Partners Limited
30 Ives Street
Chelsea
London SW3 2ND

Tel: 44-171 589 2545
Fax: 44-171 589 2622
Email: "lastname"@ferghana.co.uk

Ferghana Partners Inc.

Suite 1701
The Graybar Building
420 Lexington Avenue
New York NY 10170

Tel: 1-212 986 7900
Fax: 1-212 883 9395
Email: "lastname"

Ferghana Partners International Limited
Richmond House
12, Par-La-Ville Road
P O Box HM 1022
Hamilton HM DX
Bermuda

Tel: 1-441 296 6395
Fax: 1-441 296 6396

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