

The Pharmaceuticals- Biotechnology Interface

Partnership Strategies in a Dynamic Environment

Evolution in the sector

Today, nearly 10% of existing drugs originated from biotechnology research, and the proportion is increasing rapidly. Currently, close to 20% of all R&D efforts in the pharmaceuticals industry are taken up by the biotech/genomics industry, and this figure will double within the next ten years.

Biotechnology has arrived and is now an established player in the ethical drug value chain. Despite the recent downturns on the capital markets that have impacted the biotechnology sector, the overall growth of biotechnology within the past five years has been nothing less than spectacular.

Although initially somewhat hesitant and overwhelmed by the early dynamics of the emerging biotechnology industry, the major pharmaceuticals have embraced the sector. Surpassing the food and agricultural industry, the major pharmaceuticals have become by far the largest and most powerful revenue source for the sector.

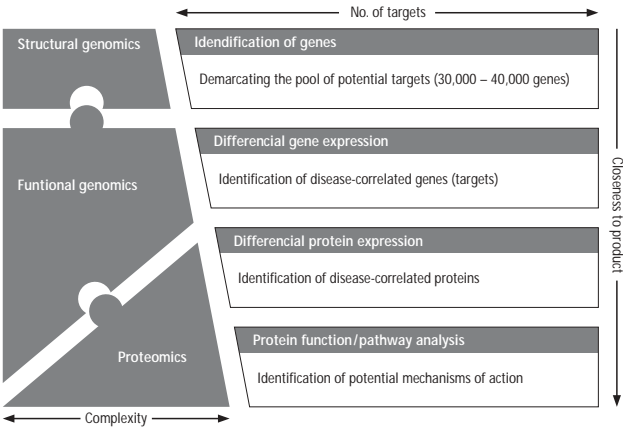
Since the early entrants moved into the market, the sector has itself undergone significant changes

Early entrants to the biotechnology sector adopted business models resembling those of the major pharmaceuticals companies – structured to take a drug from the laboratory to the patient – but only about one per cent of the early biotechs managed to raise the necessary funds to survive the high cash burn rate prior to generating first revenues from their pipelines.

Figure 1
The field of genomics comprises structural and functional information about the genome and proteome

Another vital survival characteristic of early entrants was their decision to concentrate their research on addressing unmet medical needs in areas with high demand and short time-to-market characteristics.

By picking the lowest hanging fruits, the few survivors such as Amgen, Genentech, and Biogen have accomplished market capitalization rates that resemble or even surpass those of the major pharmaceuticals.



Other players, reluctant to adopt such high risk models and seeing the moves by the major pharmaceuticals to acquire or form strategic alliances within the sector, evolved into two distinct categories.

- Drug Development Companies (DEVCOs) specializing in upstream early discovery and research around structural genomics to proteomics (see Figure 1); most of them opting not to carry the targets and leads to the patient.
- Technology Platform Providers (TECPROs) supporting the drug development process with key technologies, opting not to conduct the drug development themselves.

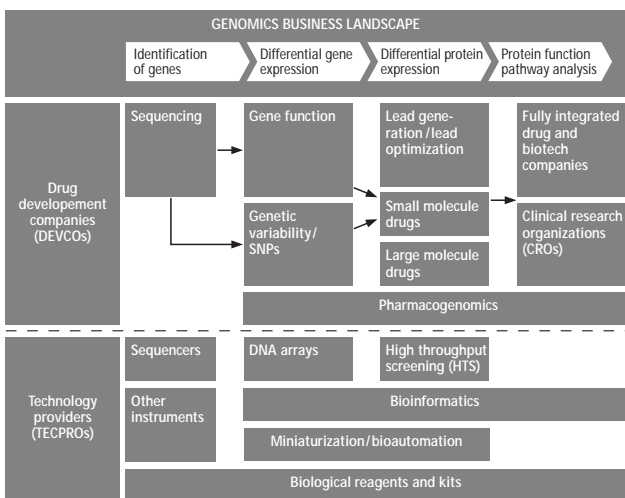


Figure 2
The genomics business landscape comprises drug development companies (DEVCOs) and technology providers (TECPROs)

These two company models represent extremes of a scale, and various mix types exist in the biotechnology business landscape today (see Figure 2).

DEVCOs tend to be specialists in various processes along the "gene-to-drug (g-2-d) pathway", ranging from experts in structural genomics applications (content providers) and companies that determine gene function, genetic variability (SNPs) and epigenomics, to companies that specialize in validation, lead generation and final clinical product development (see Figure 3).

TECPROs specialize in sub-segments, such as sequencing, high and ultra high throughput screening (HTS, uHTS), laboratory equipment/bioautomation, bio-/chemo-/pharmacophor-informatics, and biochemical reagents (see Figure 4).

The arrival of these biotech companies has yielded important and fruitful results for the major pharmaceuticals as evidenced by the many hundreds of pharmaceutical-biotechnology partnerships.

Gene-to-drug (G-2-d) pathway	Applied technologies and methods	Top Players
Identification of genes	<ul style="list-style-type: none"> • EST • PCR • Mapping • Positional cloning studies • DNA sequencing • DNA arrays • Population 	Human Genome Sciences (HGS), Millennium Pharmaceuticals, Celera, Incyte Genomics, Genset, Genome Therapeutics
Differential gene expression	<ul style="list-style-type: none"> • Transcript tagging • DNA arrays • Sequencing 	Millennium Pharmaceuticals, HGS, Curagen, Lexicon Genetics, Exelixis, Deltagen, Sangamo, Gene Logic, Quark, Orchid Biosciences, Sequenom, Variagenics, Genaissance, Genset, Pharmaceuticals, Axys Pharmaceuticals, deCode Genetics
Differential protein expression	<ul style="list-style-type: none"> • Protein chips • Maldi-TOF mass spectrometry • Giant 2-D gels 	Vertex, Praecis, Abgenix, Medarax, Morphosys, Protein Design Labs, HGS, Millennium Pharmaceuticals, Cambridge Antibody Technology, GPC Biotech, Oxford Glycosciences, Paradigm Genetics, Proteome Sciences, deCode Genetics
Protein function/ pathway analysis	<ul style="list-style-type: none"> • Protein chips • Knockout models • Transient inactivation of genes (antisense) • Transgenic overexpression models • Phage display (antibodies, peptides) 	Quintiles, Covance, Parexel, HGS, Millennium Pharmaceuticals, deCode Genetics, Variagenics, Genaissance Pharmaceuticals

Figure 3
DEVCOs traditionally specialize in the application of specific technologies

The completion of the human genome program has marked the beginning of the post-genomics era

In pharmaceuticals R&D before the human genome was decoded, less than 500 targets existed to satisfy the US\$ 300 bn plus pharmaceuticals market. With less than 500 targets, the bottleneck in the pharmaceuticals value chain has always been the generation of targets in research. With the human genome project completed and the decoding of some 30,000 genes, a major milestone for the generation of new targets was accomplished.

The generation of genomics-related data delivered new challenges for R&D in the pharmaceuticals value chain. As a consequence, bottlenecks in the value chain shifted away from upstream data generation (target identification) towards downstream data processing (target validation and lead verification) and production/scale-up (see Figure 5); the latter especially in the case of

"biologics", where the use of mammalian cell fermentation technology and animal or human-derived ingredients have a major impact.

As human science discovery is moving on, it becomes evident that key information for determining new targets is concealed in the 100,000 plus human proteins, pointing towards the human proteome as the next major challenge in human scientific discovery.

Enabling technologies	Sector of technology platforms	Top Players
	Assay technologies Reagents, kits	Qiagen, Bio-Rad, Sigma-Aldrich, Nycomed-Amersham, Invitrogen
	Bioinformatics Databases, data analysis	Incyte Genomics, Lion Bioscience, CompuGen
	Sequencers Technologies for identification of nucleic acids	Applied Biosystems, Nycomed-Amersham, Waters Instruments
	Microarray technologies Production and application of biochips	Affymetrix, Orchid Bioscience, Agilent Technologies, Motorola, Caliper Technologies, Aclara Biosciences
	High throughput screening Protein-protein interactions, SNP, 2dGE, etc.	Molecular Devices, Aurora Bioscience, Packard Biosciences, Evotec/Oxford Assymetry
	Other instruments Centrifuges, spectrometry, flow cytometry, laboratory automation, etc.	PerkinElmer, Bruker Daltonics, Luminex, Illumina

At first glance, these discoveries may appear as the long-awaited rescue from the daunting dilemma of patent expiry; however, taking this number of targets from the test tube to the patient has imposed a significant burden on downstream processes, organizations and technologies, moving beyond R&D into both the supply and commercial organizations. The major pharmaceuticals are turning their attention to addressing these challenges, looking almost exclusively to external sources, of which the biotechs form a major part.

Figure 4
TECPROs provide the technology platforms for DEVCOs and the pharmaceuticals industry

The dynamics in pharmaceuticals have influenced the shape of the maturing biotechs

Pharmaceuticals companies had primarily viewed biotech companies as a source of novel drug targets or technologies.

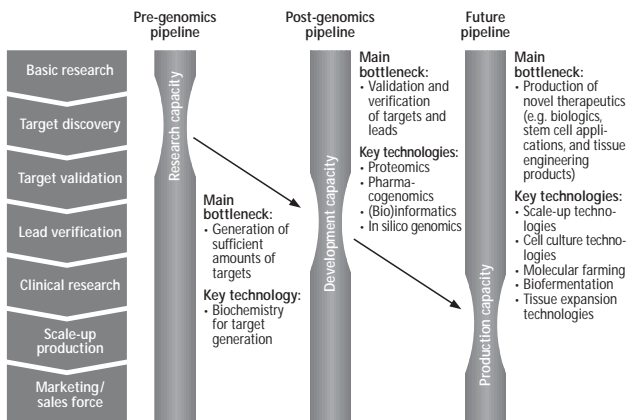


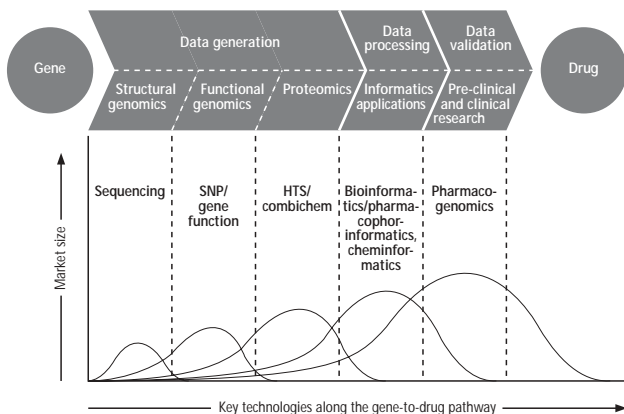
Figure 5
Bottlenecks in drug development shift downstream along the pharmaceuticals value chain

Early biotech/genomics were instrumental in the dramatic increase in throughputs, also exposing the limitations imposed by cumbersome bench research. Despite the use of conventional genomics-related technologies, efficiency yields of the two most critical resources of finance and time had only reduced spend per new chemical entity (NCE) by an average of 30% and brought an average 10% reduction in cycletime – clearly, neither of these were enough to enable companies to absorb the flood of new targets that were emerging without considerable investments.

The volume of candidates had increased so much so that it threatened to overload the existing drug development capacities.

Both the biotechs and the pharmaceuticals see the mutual benefits of addressing the issues jointly

The major pharmaceuticals are turning their attention to developing and acquiring technologies which will assist in efficient screening at affordable costs. The role of TECPROs in the provision of novel technologies that make use of in silico testing and pharmacogenomics is critical in that the latter are becoming the key assets and value contributors in the portfolio of technologies employed by pharmaceuticals companies (see Figure 6).



TECPROs enjoy short time to profitability and require relatively low investments. The challenge for TECPROs is to keep up with the fast moving, highly competitive technological developments and stay at the vanguard of innovation – or fail. This dilemma has been recognized by the capital markets, and TECPROs are under pressure to join forces in order to cover the whole value chain as has been done by Affymetrix with Orchid Bio-Science and Evotec with Oxford Asymmetry International, or to participate and become stakeholders in the drug development process.

Figure 6
The market size of key technologies increases along the individual stages of drug development

	Early discovery		Compound discovery and development			
TASKS	Target identification	Target validation	Screen development	Primary screening	Secondary screening	Lead compound optimization
APPLIED TECHNOLOGIES / METHODS	Geonomics-based biochemical research	Animal models, in vitro assays	In vitro assays	HTS, combinatorial chemistry	HTS, rational drug design	Medicinal chemistry
Time	← 1-3 years →		← 2-3 years →			
Number of compounds	N/A	N/A	10,000 compounds			
Probability of approval	N/A	N/A	← < 0,1% →			
Cost (USD m)	100-150	150-200	← 100-150 →			
Cost [%]	16%	22%	← 16% →			

Niche players can be distinguished from large multiple-technology companies such as Applied Biosystems and PerkinElmer, who recently acquired Packard BioSciences, that cover multiple sectors with technology platforms (see Figure 4). We have seen TECPROs proactively courting pharmaceuticals as an endorsement for their business performance and underlying technology.

Unfortunately, continuous investments in frequently evolving platform technologies alone will not enable the large pharmaceuticals to pull off a winning performance.

A portfolio strategy which combines lower risk investments in TECPROs with high risk DEVCOs is the right approach. The risks with DEVCO investments are the risks associated with the high attrition rates in the R&D process – the success rate of pre-clinical projects stands at only 10% (see Figure 7). Hence, investors are increasingly avoiding pure content providers, which solely rely on gene information and are moving towards integrated DEVCOs. Furthermore, spreading the stake among several pipeline products reduces the total risk. We have witnessed the

	Preclinics	Clinical trials			Approval	Manufacturing
TASKS	Pre-clinical studies	Phase I: Pharmacokinetic studies	Phase II: Dose-level optimization	Phase III: Biostatistical verification	Submission and preview	Production
APPLIED TECHNOLOGIES/METHODS	In vitro assays, animal models	Safety and biocompatibility tests in healthy human volunteers	Dose regimes, route of administration and identification testing in patients	Significance testing and further safety testing in patients	Examinations of submitted data by review board	Scale up
Time	← 1-1.5 years →	← 1-1.5 years →	← 1-2 years →	← 2-3 years →	← 0.5-1 years →	
Number of compounds	250 compounds	5 compounds			1 compound	
Probability of approval	5-10%	20%	30%	65%		(100%)
Cost (USD m)	70-90	← 100-150 →			10	50-70
Cost [%]	10%	← 16% →			1%	7%

capital markets punishing "one-product" DEVCOs with high dependency on single products (for instance British Biotech).

DEVCOs are under increasing pressure to expand further downstream into the drug-development process. Typical examples of DEVCOs that have expanded their portfolio of technologies to become increasingly integrated along the g-2-d pathway include Human Genome Sciences and Millennium Biosciences (see Figure 3). Additionally, DEVCOs aim to fill up their downstream pipelines or even, as Eisai and RheinBiotech recently did, to acquire products that are already on the market in order to prepare for the market launch of their own pipeline products.

Figure 7
Pharmaceuticals drug development is a well established sequential process consisting of several individual stages

Pharma companies can only take full advantage of biotech by establishing a highly developed pharma/biotech interface

In order to fully leverage biotech partnering potentials, it is essential for pharmaceuticals to fully understand not only the current biotech landscape with its own needs and interests, but also to anticipate future develop-

ments. The latter is of particular importance in the life science environment, which is not static but rather under constant dynamic movement.

As clinical diagnostics and pharmaco -genomics progress, personalized medicine will gain ground in the long run, and the relative importance of "one size fits all" blockbuster drugs will decline (see Figure 8). In addition, novel therapeutic strategies, such as gene therapy or stem cell-based approaches, including tissue engineering, may complement and partially replace conventional drug-based therapies.

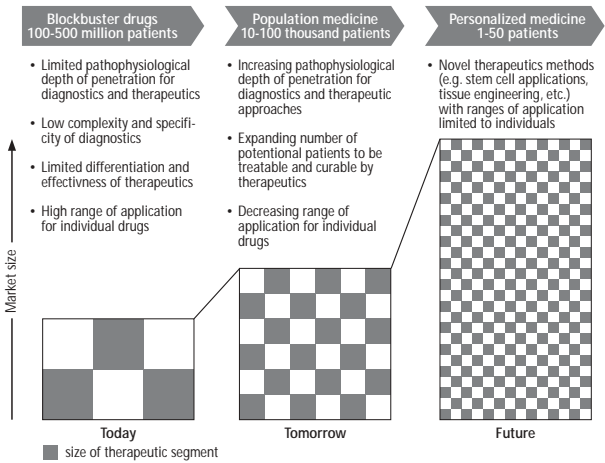
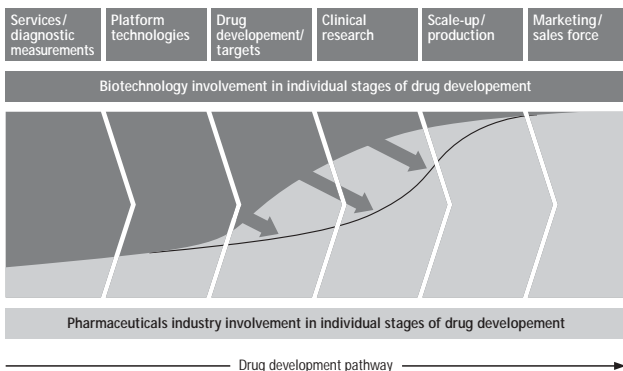


Figure 8
With increasing therapeutic specificity the pharmaceuticals market will become segmented into smaller individual markets

Furthermore, biotech companies have gained in market capitalization and critical size over the last few years, creating more mature and confident partners when it comes to negotiating dividing up the returns from pipeline products. Biotech companies also have options. They can opt for alliances with clinical research organizations (CROs) and/or established technology providers if they feel they are not taken seriously as partners and accommodated with customized solutions for their needs.

The future shape of biotech and pharmaceuticals partnerships is dynamic and opportunistic

The interface between pharmaceuticals and biotech is changing, and the organization of R&D will shift towards managing increasingly



complex processes further downstream in the drug development pathway, embracing production and the front end of marketing and sales (see Figure 9). The shift of biotech companies towards downstream drug development and pharmaceuticals' increasing focus on blockbusters creates new space for mutual interest and, hence, partnerships. Thus, pharmaceuticals companies that are well positioned in downstream processes will have strong negotiating power when it comes to securing marketing rights for future blockbuster drugs.

Adapting to this changing environment means that modern biotech partnering will no longer be outlined by one-dimensional interaction revolving around buying and selling classical drug targets or technology, but rather by a comprehensive, multifaceted interface that will demand a sophisticated approach from pharmaceuticals.

Figure 9
The pharmaceuticals/biotechnology interface is continuously shifting downstream along the drug-development pathway

Moreover, as DEVCOs seek to extend their activities further downstream into the drug development process, they represent potential partners to provide additional capacity for the drug-development process.

Other strategies include more dynamic in-licensing as well as out-licensing strategies for products in the R&D portfolio to enable pharmaceuticals companies to prioritize their portfolio and to extract maximum leverage from existing capacities

Winning strategies ...

Winners in the future will be those who develop the capability to build and dismantle partnerships in response to changing therapeutic/product portfolios.

To install and build up such alliances, there are a number of critical success factors:

- Defining and managing the matrix between the therapeutic/product mix on one axis and the stages in the gene-2-drug pathway on the other to identify needs and overlaps (see Figure 10)
- Building R&D portfolio management capability that actively leverages in-licensing and out-licensing options
- Having an integrated and dynamic "bottle-neck-management" feedback loop extending from target discovery to scale-up production and product marketing
- An organizational model which promotes efficiency across, "virtual organization" boundaries
- Building a quality and professional partnership culture motivated by mutual success

Core groups of pharmaceuticals company X →

	Core group A	Core group B	Core group C	Core group D	Core group E	Core group F	Core group G
Structural genomics (sequence purveyors)	Gap 1	Gap 2	Gap 3	Partner A	Gap 4	Gap 5	Gap 6
Differential gene expression (positional cloners; HTS; DNA chips)	Partner B	Partner B	Partner B Partner C Partner D	Partner B	Gap 7	Gap 8	Gap 9
Differential protein expression (functional genomics; HTS; protein-chips bioinformatics)	Partner B Partner E	Partner B Partner E	Partner B Partner C Partner E	Partner B Partner E	Gap 10	Partner E Partner F	Gap 11
Proteomics (HTS; combinatorial chemistry; pharmacophorinformatics)	Gap 12	Gap 13	Gap 14	Partner G Partner H	Partner I Partner J	Partner G Partner H	Gap 15
Drug development (drug delivery; clinical trials; pharmacogenomics)	Partner K Partner L	Partner M	Partner K Partner N Partner O	Gap 16	Partner P	Gap 17	Partner Q

Process flow of "g-2-d" ↓

- Investment in and recognition of new skills and competencies outside of the sciences, such as those of information brokers and partnership managers – putting a stronger focus on managing skills in addition to research and scientific know-how in R&D departments
- Efficient management of IT within the new "virtual organization", responsive to handling issues from database compatibility to scientific data modeling and the protection of proprietary information

The establishment of an efficient pharma/biotech interface is a far reaching process that requires an integrated approach across many functions within the existing organization. Input will be required from corporate management, business development, R&D, production, marketing, and IT functions. To handle this level of complexity in a competitive time frame, a structured and well coordinated implementation process is essential.

Obtaining tangible as well as sustained results is a process that requires a high-level of commitment from all sides.

Figure 10
A matrix projection of biotech partnerships along the g-2-d pathway will reveal potential gaps or overlaps

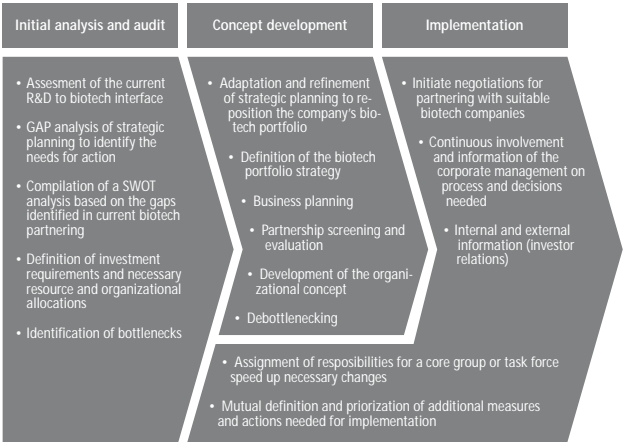


Figure 11
A three-step approach has proven successful for creating and implementing an effective and fast-acting pharmaceuticals/biotechnology interface

An approach

At Roland Berger we have developed a three-stage process, comprising initial analysis, concept development and implementation phases (see Figure 11). The approach has delivered successful results as endorsed in client testimonials.

At Roland Berger we have the capability and experience to collaborate successfully with the many and diverse businesses which can be engaged in such work.

If you need any further information or would like to discuss your options to develop, revisit or implement a pharma/biotech strategy, please contact Roland Berger Strategy Consultants.

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