

# What Does Big Pharma Want From Biotech?

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## Executive Summary

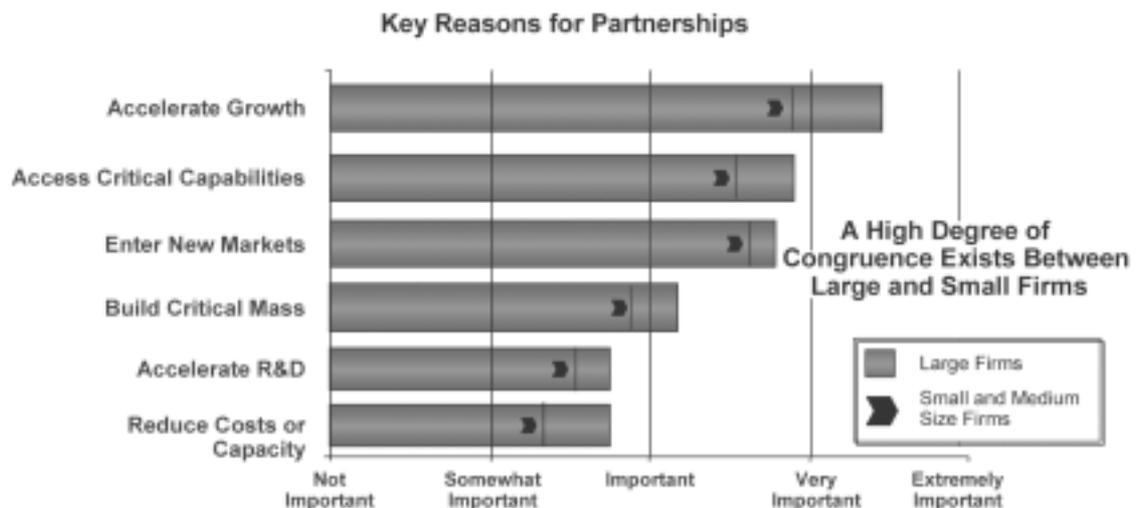
What does Big Pharma want from biotech? Exactly what it wants from its own internal discovery group — a patent-protected, innovative product representing the “next big wave” in a therapeutic area with high unmet medical need and commercial value, and one that is discovered and developed by a flexible, goal-driven team with scientific expertise and commercial foresight. Simple as this sounds, it is not easily achieved, hence the search beyond the internal corridors of Big Pharma to the outside world for that “diamond in the rough”. The search continues through the voluminous laboratories in start-up Biotech, the alcoves in universities, and the cushioned conference rooms of venture capitalists. Once found, the investigative process continues through a thorough due diligence, an intricate negotiation, and an entwining alliance to begin the tortuous road from drug development to marketed product. Along the way, care is taken to select the right partner, choose the correct deal structure, align competing objectives, and establish the relationship that will (hopefully) weather the tumultuous storms ahead.

## Challenges of the Pharmaceutical Industry

Big Pharma faces many challenges: shrinking pipelines, pricing pressures, reimbursement hurdles, increasingly stringent regulatory requirements, increased competition, high promotional expenses, demand for pharmaco-economic analyses, hostile consumer groups (at times), skeptical governments, a need for a steady source of products with high commercial potential, and unblinking critical eyes on quarterly reports in the public sector.

These challenges overlay a changing landscape in the pharmaceutical industry characterized by industry consolidation and an ageing population driving market growth, a preponderance towards direct-to-consumer promotion (at least in the US), open internet access to business personnel, providers and consumers, and an explosion in genomic research that may significantly alter how future therapeutics are eventually prescribed and that may catapult the drug device/testing industry into a new forum — “personal pharmaceuticals”.

## Why Partner?



Source: Association for Corporate Growth/Booz+Allen & Hamilton/ELNIZ

The need for growth drives the industry and represents the most significant factor in both large and small firms seeking alliances. There is an insatiable need to fill pipelines with potential blockbusters that will guarantee its leadership among its peers. In fact, Big Pharma/Biotech Collaborations will continue to proliferate since both types of companies need each other to fully explore the frontiers of science as no one company can do it all. This is validated by the number of alliances formed from 1995 to mid-2000. Pharma and Biotech companies established 2,661 alliances collectively valued at more than US\$28 billion (*Pharmaceutical Executive*, March 2003). A sample of recent alliances and their associated deal value incorporating upfront fees and various milestones is shown on the next page.

## Alliances Between Pharmaceutical Companies, Large and Small Is a Growing Practice

Discovery Stage	Early Stage (Preclinical, Phase I)	Late Stage (Phase II, III)
<ul style="list-style-type: none"> <li>Onyx / Bayer – Ras inhibitors \$75MM</li> <li>HGS / SmithKline – Gene sequencing \$125MM</li> <li>Regeneron / P&amp;G – broad discovery program \$135MM</li> <li>Vertex/Novartis \$800 MM</li> <li>Millennium / Abbott – Obesity / Diabetes \$250MM</li> <li>Millennium / Aventis – Inflammation, \$450MM</li> <li>Curagen / Bayer – Obesity and Diabetes - \$750MM</li> <li>Exelixis / GSK - cancer, inflammation, vascular conditions \$455M</li> </ul>	<ul style="list-style-type: none"> <li>Neurogen / Pfizer – NG295-1 \$59MM</li> <li>Genasera / Genentech – IL-9 \$68MM</li> <li>Corvas / Schering Plough – Thrombin inhibitors \$80MM</li> <li>British Biotech / Serono – Metalloenzyme inhibitors \$80MM</li> <li>Vertex / Schering AG – VX-853 \$88MM</li> <li>GenVec / Parke-Davis – VEGF \$100MM</li> <li>Regeneron/Aventis – VEGF Trap \$450 MM</li> <li>Amgen/Biovitrum – BVT 34 98 \$600 MM</li> </ul>	<ul style="list-style-type: none"> <li>SuperGen / Abbott – Rubitecan \$150MM</li> <li>ICOS / Lilly – Cialis \$180MM</li> <li>OSI / Genentech / Roche – Tarceva \$100MM</li> <li>Adolor / GSK – Avimopan \$270MM</li> <li>Cellect / Pharmacia – mAb for RA \$280MM</li> <li>Aviron / Wyeth – FluVist \$400MM</li> <li>Genia / Aventis – Genasense \$480MM</li> <li>Amylin/Lilly – Esendin \$325MM</li> <li>Neurocrine/Pfizer – Indiplon \$ 400 MM</li> <li>EyeTech/Pfizer – Macugen \$745 MM</li> </ul>

Source: Recombinant Capital, Mithover

Given the probability of success of drug candidates reaching the market (Table 1), it is clear that Big Pharma cannot rely solely on its internal programs to supply a pre-blockbuster line-up, hence the need for acquiring compounds from other sources via joint development agreements, licensing or standard acquisitions.

**Table 1. Probability of Success versus Development Phase**

Phase	Pre-clinical	Phase I	Phase II	Phase III	Registration
Probability Of Success	7%	23%	33%	73%	95%

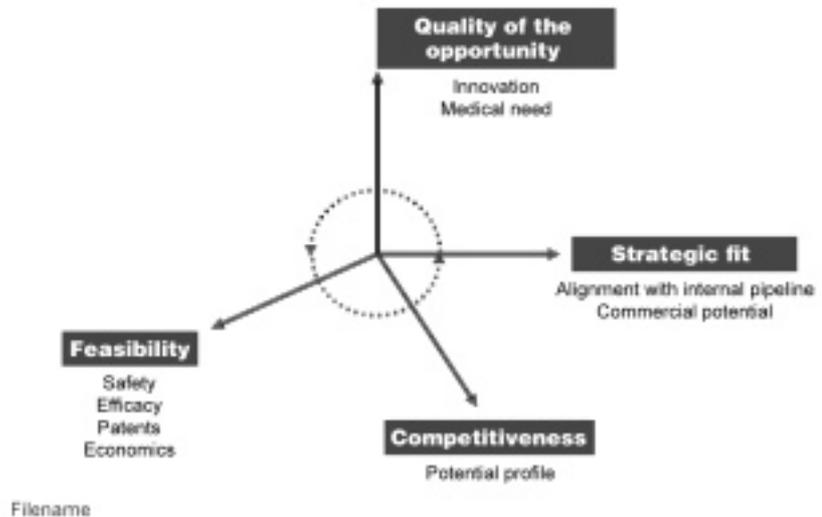
Average percentages taken from a variety of industry standards.

### How Big Pharma Decides What It Wants

There are four critical elements that guide the selection of compounds for Big Pharma: strategic fit, quality of the opportunity, feasibility and competitiveness — all contributing to the overall economics of the opportunity. Significant effort is expended in designing a strategy that will ensure growth and productivity over the long-term and that capitalizes on the strength of the organization. This could encompass primary care products associated with high field force costs and engagement, specialist products that are targeted to a smaller audience, or a combination of both. It could build on existing strengths or set a goal for entry into an entirely new therapeutic area based on whether the product is truly innovative or fulfills an unmet medical need. Key to this decision is the ability to identify “the next big wave” in the therapeutic treatment of a particular disease, a significant product attribute in an existing class, or a need that is not fulfilled by currently available drugs. Although strategies are designed to set corporate direction, the most successful organizations are those that are fluid enough to pay heed to the opportunistic or chance occurrence of an unanticipated opportunity. This flexibility in changing direction rapidly is key to success and needs to permeate the entire organization. However, often it is the project scientist, clinician or marketer who is closest to the customer who will first sniff the winds of change and evaluate potential drug candidates in light of their overall product

profile, efficacy, safety, patent life, anticipated cost and expected return. Finally, drug candidates are reviewed with regard to the competitive environment, i.e. strength of the competing companies, position in the marketplace, order of entry, promotional spend and share of voice.

## Opportunities Are Regularly Evaluated Along Four Dimensions



## Process of Search & Evaluation

Big Pharma uses a web of entities to source external compounds or technologies. Although personal contact is and always has been the best vehicle to establish communication, internet access has brought even the most remote opportunities to the forefront through search functions, web pages, commercial databases, etc. Nonetheless, the preemptive company will engage in a proactive

## Creating Licensing Networks Through a Variety of Sources



effort using a variety of sources to expand its portfolio, such as contacting small to medium size companies, Biotech start-ups, universities, and venture capitalists. The interactions are set to initiate contact, establish relationships, exchange ideas, sort through priorities, communicate each party's strengths and needs, and identify best-fit scenarios.

When contacting Big Pharma to solicit interest, it is helpful to present the opportunity in a way that will create generate the most excitement and expedite the review. Preference is given for an alliance involving a drug candidate or platform technology that incorporates some of the desired characteristics below:



#### S&E: Target Licensing Opportunity

- New chemical entity
- Worldwide rights available
- Compound in clinical development (or end of pre-clinical)
- Fits disease strategy of Pharma

The technology, lead compound or drug candidate should be able to produce a compound that has a unique selling point or product attribute that most clearly will produce patient benefits and become competitive in the marketplace. The most desired compounds are typically late stage, although compounds with new mechanisms of action (MOA's) theoretically conferring additional patient benefit versus marketed compounds are desired and actively sought. Compounds with different MOA's likely will produce different tolerability and safety profiles, as well as (hopefully) better efficacy, thus increasing the health practitioner's armamentarium to account for individual needs.

### Pharma Strategy Identifies Future Market Opportunities



Additionally, the compounds should have adequate patent life internationally and represent a new chemical entity (NCE) with broad but defensible claims for both structure and indication. The deal structure should incorporate global rights to multinationals in order for the company to maximize its contribution to the clinical development, regulatory, marketing and sales effort. The importance of a uniform global message, coordination of launch and promotional activities, and relationships with health authorities as well as key opinion leaders worldwide cannot be underestimated.

### **Big Pharma's Key Interests**

- Class and Mechanism of Action
- Expected Indications
- Development Stage and Next Milestone
- Dosage
- Technology or Compound: Key Differentiator
- Competitive Position
  - Top 2-10
  - Order of entry
  - Key attributes
- Expected Launch
- Data
- Intellectual Property Position
- Production Issues
  - Current/anticipated
  - Biologics system or small molecule
  - Current cost of goods
  - Packaging
- Deal Structure Proposition
  - Type (licensing/other)
  - Territory

In the first presentation of the opportunity to Big Pharma it is helpful for a Biotech to summarize the key messages as described above. A succinct overview in a non-confidential document accurately describing the drug candidate will expedite the review process and highlight the parameters on which Big Pharma makes its decisions. Layering the correspondence with an upfront executive summary followed by increasing amounts of detail in electronic form is the preferred mode of interaction. A face-to-face meeting, teleconference or videoconference with key business and technical personnel following the electronic submission is a useful follow-up.

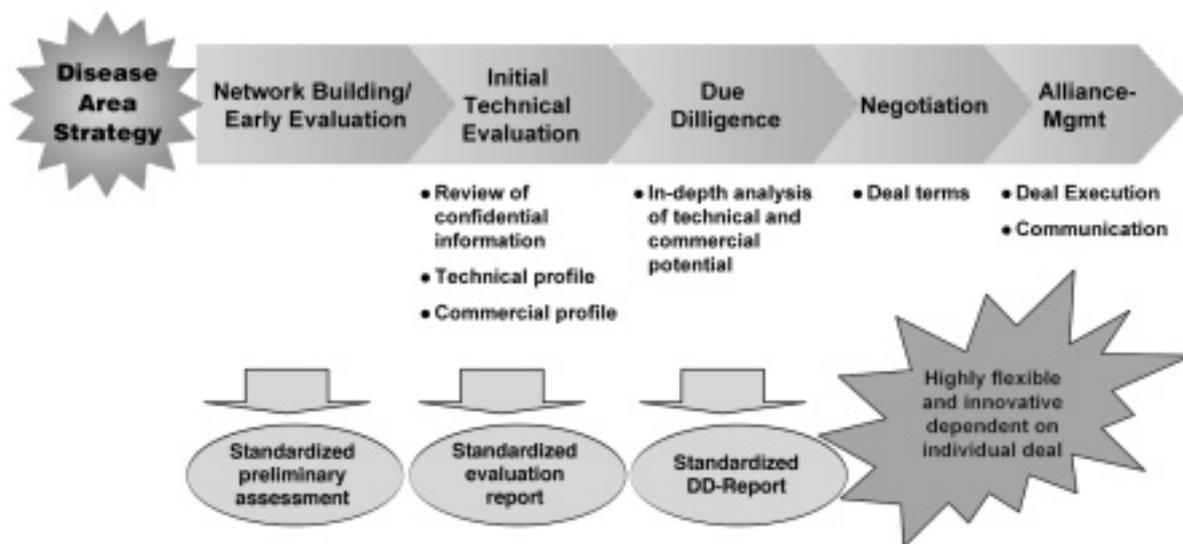
Although late stage compounds are clearly the most desired, the proposed alliance also may incorporate various modalities, research and development skills, manufacturing and supply, or commercial considerations that go beyond the single product or technology transaction. In this type of alliance, which may take the form of a majority or full ownership, such as the partial acquisition model or a complete acquisition, respectively, a more complete evaluation is required. These types of transactions extending to a more involved corporate liaison on a company-wide basis encompass an in depth due diligence, including but not limited to a financial and legal evaluation of the company, and must contribute an intangible beyond the product or technology license alone.

### What's Eye-catching in Today's Universe?

- Late stage clinical pipeline
- Platform technology that delivers a stream of innovative compounds in key disease areas
- Adequate financial structure
- Experienced management
- Scientific reputation
- Track record of partnering
- Survival skills

Adequate financial structure, experienced management, scientific reputation, a track record of productive relationships, and overall survival skills are key to moving the alliance beyond the compound or technology license into a mutually productive relationship. Considerations for choosing the appropriate deal structure will be discussed later.

### Proactive Standard BD&L Process



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Once Big Pharma’s key interests have been piqued via disclosure of non-confidential information and an initial technical evaluation (ITE), the evaluation process may take on a more formal role. This involves a critical assessment of benefits and risks following the execution of a confidential disclosure agreement (CDA) and a due diligence assessment by a team of functional experts comprising, but not limited to, representatives from research, clinical development, marketing, patents, technical product development, commercial product development, legal and finance. An exhaustive review follows, culminating in the final due diligence report which recommends either pursuit or rejection of the opportunity.

## Standard Processes and Team Work



Significant details of the product or licensor company history is considered and documented in a full length due diligence report containing an in depth analysis of product risks, benefits, and commercial implications involving a variety of “what if” scenarios that form the basis of three possible forecasts, i.e. base forecast (most likely to occur), optimistic forecast (if the best scenario occurs) and pessimistic forecast (if the worst scenario occurs). The final recommendation is distilled to a few very basic tenets as described below which provides the criteria for the Go/No Go decision.

**“Is This the Right One?”**

<p><b>Scientific Rationale</b></p> <ul style="list-style-type: none"> <li>• Does it make scientific sense?</li> </ul> <p><b>Efficacy</b></p> <ul style="list-style-type: none"> <li>• Does it work?</li> </ul> <p><b>Liability Risk</b></p> <ul style="list-style-type: none"> <li>• Is it safe?</li> </ul>	<p><b>Market potential</b></p> <ul style="list-style-type: none"> <li>• Can I make money on it?</li> </ul> <p><b>Strategic fit</b></p> <ul style="list-style-type: none"> <li>• Will it enhance my growth?</li> </ul> <p><b>Economics</b></p> <ul style="list-style-type: none"> <li>• Can I afford it?</li> </ul>
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## Considerations for Partnering

As described earlier, the most frequent reason both large and small companies establish alliances is to fuel company growth. However, the type of alliance chosen requires reflection not so much on the external object but within the depths of the company soul. The first step in the process is a critical self-analysis of the licensor's internal strengths and weaknesses. Only then will the correct deductions be made. Too often the small Biotech rushes forward to design an alliance which will allow it to rapidly fulfill its ultimate corporate goal, becoming a FIPCO (fully integrated pharmaceutical company), without regard to the stepwise growth that is critical for success. In designing the alliance with Big Pharma, undue pressure is often put upon the negotiation for the inexperienced partner to control processes where there is no experience or demonstrated expertise. In the same vein, Big Pharma often needs to step back from its "Best Practices" mode of operation to control all aspects of the process and allow flexibility and an open mind to the potential partner's views. Success is more likely to occur when both parties contribute what they do best in an unfettered fashion ultimately ensuring that the mutual goal of both parties — maximizing commercial success — is attained.

### Basic Rules for Finding the Ideal Partner

Know yourself  
Know what you need  
Know what to look for

And when you find the perfect partner:  
Be creative

## Choosing the Correct Deal Structure

A variety of deal structures exist which can accommodate the needs of both parties. However, as mentioned earlier, the priority should be capitalizing on each party's expertise and learning from the other party rather than demanding control over functions where there is no demonstrated expertise. For example, the Biotech may be anxious to achieve its FIPCO goal and therefore demand the right to market the product when no such infrastructure currently exists. On the other hand, Big Pharma may wish to control Research direction when clearly this is the contributing expertise of Biotech. Both need to step back and reassess their respective contributions and model the deal structure appropriately. On the other hand, if the case exists where Biotech supplies drug product and/or drug substance from cGMP, FDA-approved facilities that are already in operation, an alliance with Big Pharma who has global reach in terms of clinical, regulatory, sales and marketing could be extremely successful and is the type of alliance that plays to each parties' strength.

## The Menu of Deal Structures

**In-licensing** = "I can use it"

**Out-licensing** = "I still own it, but you can work on it"

**Strategic Marketing Alliances** = "We sell together"

- **Co-Promotion:** two companies, one brand, collaborative relationship
- **Co-Marketing:** two companies, two brands, competitive relationship

**Biotech Alliances** = "I'll discover it, you develop, market and sell it; maybe we'll even do it together"

**Partnerships** = "We do some things together"

**Joint Venture** = "Let's start our own company"

**Product Divestment** = "You can have it all"

**Mergers and Acquisitions** = "We are one" or "I own you now"

Source: C. Fischette, American Pharmaceutical Review, in press (2004).

## Common Deal Parameters

Although no two deals are exactly alike, typically license agreements involve an upfront payment, milestones and royalties in exchange for the right to develop, market and sell. Sometimes, more advanced products in clinical development demand higher upfront fees and the price generally has increased over time as in-licensing and alliances have proliferated in the industry. Deal complexity is rising and upfront fees may include not only cash, but equity as well.

Clinical development and commercialization costs are often shouldered by Big Pharma. However, some deals are constructed with the Biotech paying 50% of development costs with a corresponding increase in return.

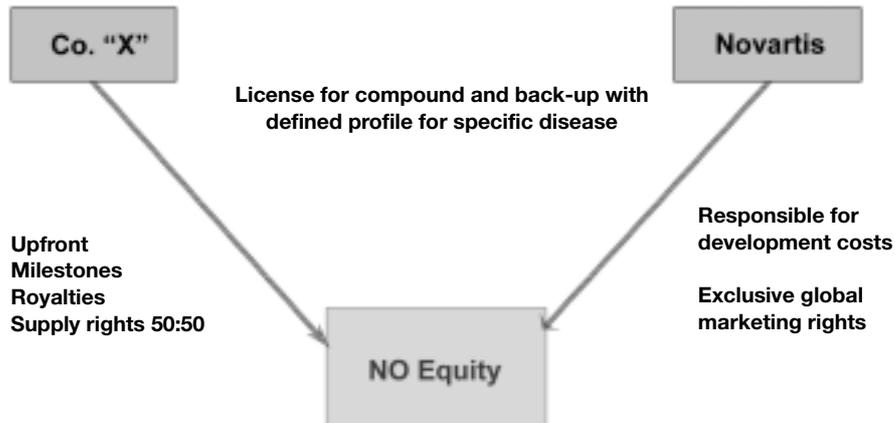
Generally compensation extends from typical royalty arrangements to profit share agreements where the profit is distributed according to each party's contribution to intellectual property, clinical development and commercialization costs. A higher commitment to funding, which equates to taking a higher risk, insures a greater share of the profit.

The deal construct will vary depending not only on the ability to pay, but also *should* vary depending on the demonstrated expertise of each parties' contribution.

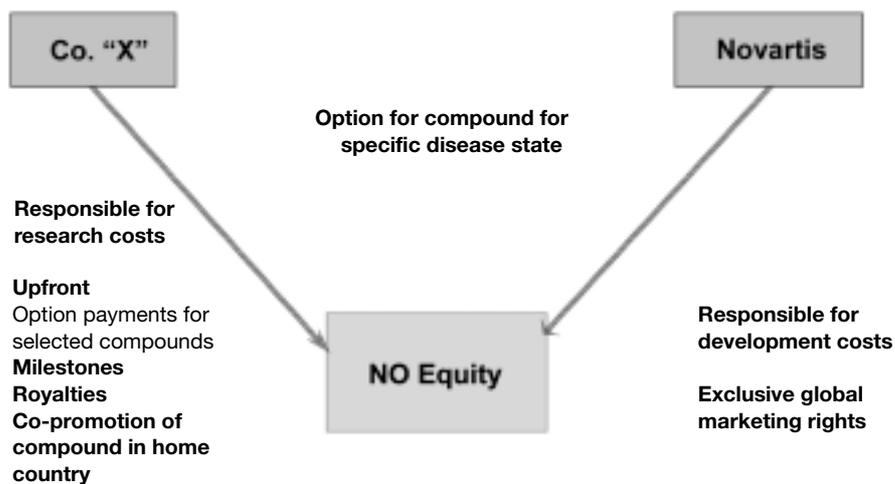
## Deal Structures

Because no "one-size-fits-all" solution exists in the business development universe, a variety of structures speak to the fluidity of companies in constructing alliances that meet individual corporate goals. Below are listed a sample of examples from recent deals involving Novartis that demonstrates a variety of deal constructs:

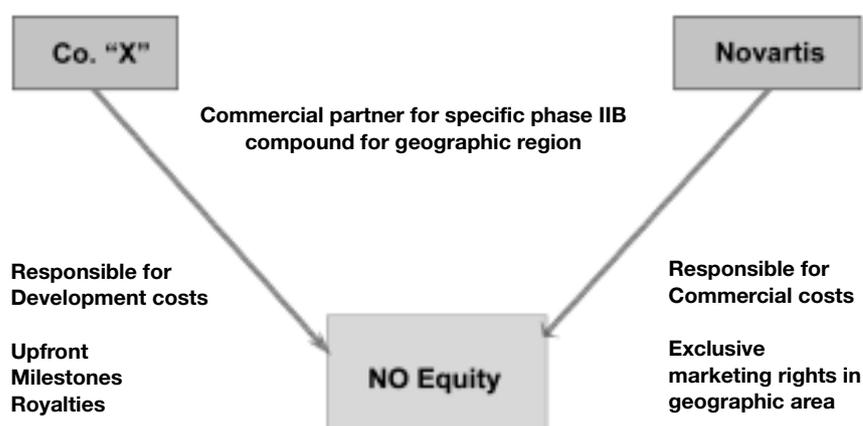
## Research Collaboration – License Example



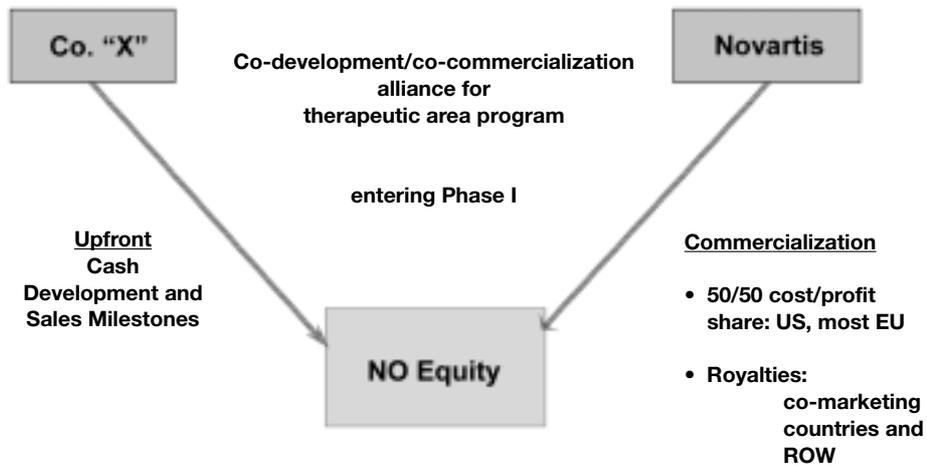
## Research Collaboration — Option Example



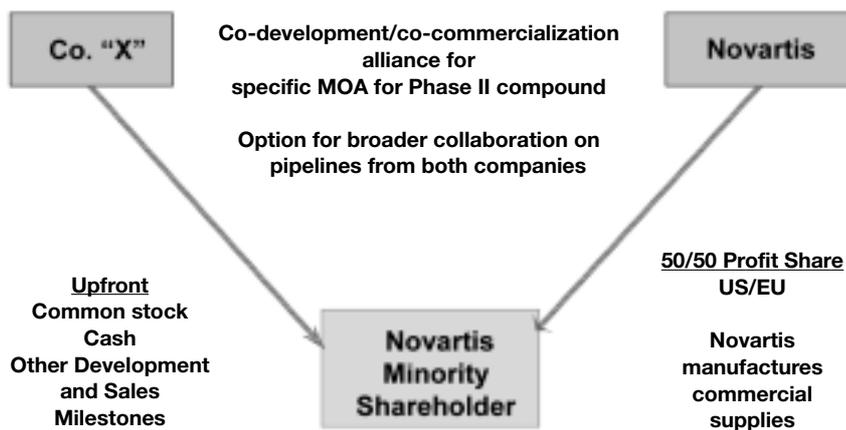
## Exclusive Commercialization — Example



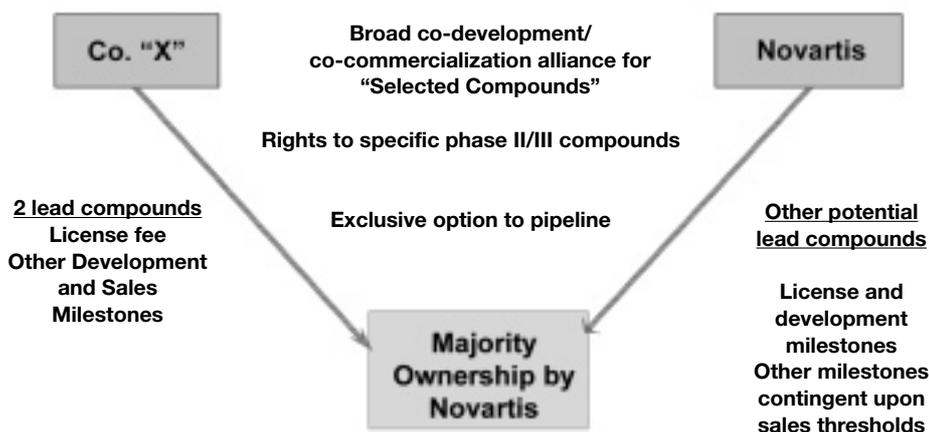
## Extended Collaboration Non-Equity Model — Example



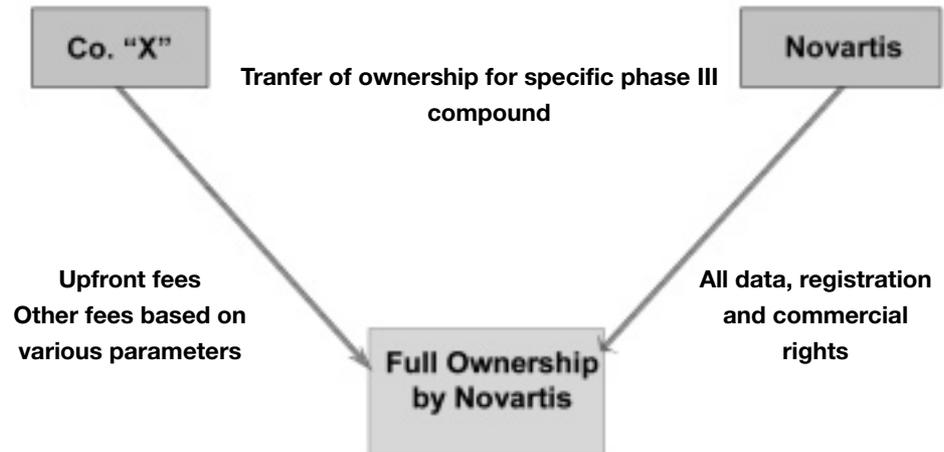
## Minority Shareholder — Example



## Partial Acquisition — Example



## Product Acquisition — Example



Finally, outright acquisitions may extend to a specific product, as in the acquisition of the Phase III product darifenacin by Novartis, or to a company, as in the case of Pfizer's well publicized merger-acquisition of Warner-Lambert, Pharmacia and Esperion, or Johnson & Johnson's acquisition of Scios.

### Elements of the Deal

The definitive transaction establishes the rights, roles and responsibilities of each party with respect to the proposed transaction, as well as defining paths for addressing risks and contingencies. It is useful to base the agreement on a clear understanding of each parties' objectives, strengths and complementary abilities before "pen goes to paper". A preliminary development plan designating operational control with proposed timelines and costs should be incorporated into the agreement to establish roles and to help speed implementation of the deal by the respective work teams. The initial development plan should incorporate marketing objectives in order to support the possible product claims to be made at launch.

### Putting the Deal Together

#### Elements of the Deal

- Structure
- Development
- Cost and Profit Sharing
- Regulatory Responsibilities
- Intellectual Property Ownership/Management
- Economic opportunities
- Governance
- Exit provisions

The companies should give thought to future opportunities that could generate significant economic value, such as, combination products or other formulations that could extend into a life cycle management program thus generating additional revenue.

Governance is another challenging area in the negotiation process. The formation of a Joint Product Committee composed of representatives from project management, clinical and marketing to address operational aspects of the alliance and a Joint Steering Committee to approve budgets and resolve disputes are common mechanisms for co-development/co-commercialization agreements. Dispute resolution generally takes the form of resolution by escalation to executives of the companies, arbitration or litigation.

Termination and exit provisions are usually one of the more difficult areas in the negotiation process, since divorce is difficult to accurately picture when marriage is being contemplated. Nevertheless, careful apportionment of contributing elements and fair compensation for their value needs to be taken into consideration. The right to terminate for breach, change of control, or data that is non-conforming to the originally projected target product profile, as well as a company's sole right to terminate for any reason must have provision in the contract designating consequences of termination for each scenario. In general, the non-terminating party may receive rights to effectively continue product development and commercialization, while the terminating party receives fair compensation for prior contributions (usually in the form of a residual royalty).

### Pitfalls

Although much care and thought will be taken throughout the negotiation process to accommodate multiple scenarios, the unfortunate fact remains that more alliances fail than succeed. While product failures and unfavorable market conditions account for termination in most cases, poor communication ranks second. Big Pharma's intricate committee structure and stepwise process versus Biotech's rapid decision-making and eagerness to proceed to the next stage is often the source of intense discussion. In addition, poorly defined roles or negotiated terms, ineffective alliance leadership, weak commitment, cultural differences or senior management changes can all contribute to the failure of an alliance.

#### **Alliance Failures : "Poor Communication"** *A manageable problem ranks among highest reasons for Alliance Deal Failures*

■ <b>Product failures / drastic market changes</b>	<b>71%</b>
■ <b>Poor partner communication</b>	<b>57%*</b>
■ <b>Other major reasons for alliance failures include*:</b>	
• <b>Poorly negotiated terms</b>	<b>43%</b>
• <b>Poorly defined partner roles</b>	<b>43%</b>
• <b>Ineffective alliance leadership</b>	<b>43%</b>
• <b>Weak internal and external commitment</b>	<b>29%</b>
• <b>Cultural differences</b>	<b>29%</b>
• <b>Senior Management changes</b>	<b>14%</b>
■ <b>Can and should be managed by Alliance Management</b>	

\* Cutting Edge – Pharmaceutical Alliances Licensing and Deal-Making Survey - 2003

## Conclusion

Although competing objectives may exist between Biotech and Big Pharma in terms of seeking an alliance to validate the company for the former or fill a pipeline gap for the latter, the prospective alliance can fulfill its combined objective of bringing to market a commercially successful product if enough foresight and flexibility is incorporated into the relationship. The process first involves a critical self-appraisal of one's inherent strengths and weaknesses, and then the choice of a partner and appropriate deal structure that accommodates those strengths and needs. Care must be taken to ensure that the deal is constructed not based fully on corporate goals of one partner, but more so on achieving what neither party could have on its own. Finally, communication is key to alliance success, as it is with all interpersonal relationships, domestic and otherwise. ■



## About the Author

Christine is Executive Director, Global Business Development and Licensing at Novartis Pharmaceuticals Corporation in East Hanover, New Jersey. She has 20+ years experience in the pharmaceutical industry and has been actively engaged in all stages of drug development from concept to marketed product. Her breath spans bench level research at Hoffmann-La Roche through several functions at Pfizer with increasing responsibility for clinical development (Phase I-IV), project management (IND/NDA submissions), medical marketing (strategy and implementation), marketing (head of US commercial division for diabetes) and business development (multiple transactions). In her present capacity at Novartis she has identified, negotiated and executed a number of deals with both Biotech and Big Pharma incorporating a variety of deal structures including royalty-bearing licenses, profit share agreements with co-development/co-commercialization structures, supply agreements, and a partial acquisition. Christine received her B.A. at Rutgers University, Ph.D. at the University of Medicine and Dentistry of New Jersey and earned a Post-Doctoral Fellowship award at Rockefeller University. She has authored a number of original research publications, including a publication in Science.

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