

ANALYSIS OF STRATEGIC ALLIANCE DEALS IN THE GLOBAL CNS INDUSTRY

by

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ABSTRACT

The therapeutics market for central nervous system (CNS) disorders is projected to grow substantially over the next ten years. This growth is mainly attributed to the increasing proportion of the ageing population, especially in western countries. Pharmaceutical and biotechnology companies in this industry will continue to form strategic alliances.

This review examines the attractiveness of the CNS drug industry and identifies key success factors for the sector. The study further analyzes deals transacted in the CNS area over the past 5 years. The purpose of this analysis is to understand the factors that influence deal size and the cost-benefits of pursuing certain indications.

The deals are segmented according to stage of drug development. Suggestions are made as to what a small biotechnology company needs to do to attract partners. This study identifies applicable deals that may be used for benchmarking by a small biotechnology company in the CNS industry.

DEDICATION

This Project is dedicated to my wife Pam, and our children Ray, Stephanie and Chris for being a source of inspiration.

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1 INTRODUCTION

1.1 The Purpose of Biotechnology-Pharmaceutical Alliances

Alliances and collaborations play a major role in the survival and growth of small biotechnology companies. Strategic alliances enable small biotechnology firms to gain access to financing and specialized resources. On the other hand, alliances allow big pharmaceutical companies to obtain new product candidates for their development pipelines and to gain entry into new therapeutic areas (Audretsch and Feldman, 2003). Growth of small biotechnology firms is, therefore, largely determined by their ability to develop alliances with big pharmaceutical companies that will offer financial resources, manufacturing, marketing and regulatory expertise (Niosi, 2003). In fact, the market success of a biotechnology firm is influenced not only by its ability to develop new product candidates, but also to a large extent by its relational capability (Chiesa and Toletti, 2004). Due to the competitive nature of the industry, with many companies competing for scarce capital, emerging biotechnology firms need to follow a series of nearly inevitable steps. First, they need to secure patents to protect their intellectual property (IP) and to signal their worth to potential financing sources. Second, they should obtain venture capital and conduct efficient research and development (R&D). Third, they require an alliance with a big pharmaceutical company to develop and commercialize their products (Niosi, 2003).

1.2 Drivers of Biotechnology-Pharmaceutical Alliances

According to Audretsch and Feldman (2003), creation of alliances depends on three factors, namely capabilities, control and context. Capabilities determine whether a firm can develop, manufacture and commercialize products. Control gives a company the right to apply these capabilities. Context, on the other hand, includes the external environment in which an

enterprise functions. For instance, Stuart and Sorenson (2003) reported that geographic proximity to established companies, industry experts and venture capitalists affect the performance of biotechnology firms. If one of the three factors - capabilities, control and context - is deficient or weak, a company will have reasons to enter into an alliance. Moreover, small biotechnology firms are faced with problems of uncertainty, asymmetric information and high transactions costs which make it difficult for them to obtain financing from capital markets (Audretsch and Feldman, 2003). As a result, strategic partnerships are crucial for small biotechnology firms.

1.3 Benefits of Biotechnology-Pharmaceutical Alliances

Alliances are of great value to the participants because the synergies between the firms allow them to exploit their competitive assets, avoid duplication of tasks and advance economic efficiencies (Audretsch and Feldman, 2003). Small biotechnology firms are highly proficient in innovative research, and this could be attributed to their size, flexibility, entrepreneurial environment and links to creative thinkers at universities and other research institutions (Tyebjee and Hardin, 2004). Alliances, therefore, enable small biotechnology firms to focus on their core competencies of technological innovation, to decrease financial risks and development costs, and to offset the liabilities of gaining production and commercialization capacity. The objectives of small biotechnology companies in alliances are to secure funding, and to validate and commercialize their technology with negligible dilution of their stock (Tyebjee and Hardin, 2004). On the other hand, alliances enable large pharmaceutical companies to circumvent the uncertainties in biotechnology research and to decrease exposure to potential legal liabilities. The objectives of big pharmaceutical companies in alliances are usually to broaden their product development pipeline by gaining control over new drugs being generated outside their firm with minimum risk exposure (Audretsch and Feldman, 2003).

1.4 Strategic Basis of Biotechnology-Pharmaceutical Alliances

According to Tyebjee and Hardin (2004), the strategic basis of alliances between small biotechnology firms and big pharmaceutical companies is a result of three key factors. First, the alliance participants bring complementary competencies that are needed for drug development. For instance, a small biotechnology firm's technological innovation complements a big pharmaceutical company's expertise in regulatory approval and commercialization. Second, the alliance members supply different assets to the relationship. The biotechnology firm provides an innovative technology and the pharmaceutical company supplies the funds for development, approval and commercialization. Third, alliances enable the risks of new drug development to be apportioned to the most appropriate financial market. For example, the high risks of early stage drug development are shouldered by the venture capital investors, while the lower risks of later stage drug development are carried by big pharmaceutical companies whose shareholders are somewhat risk averse.

1.5 Stage of Biotechnology-Pharmaceutical Alliances

Biotechnology-pharmaceutical alliances have become increasingly common over the past forty years (Hagedoorn, 2002). The number of biotechnology-pharmaceutical alliances for clinical stage and marketed products showed a marked growth from 38 in 2002 to 68 in 2004 (Chaya, 2005). This supports the notion that pharmaceutical companies are increasingly looking for clinical drug candidates from biotechnology firms to fill their dwindling product pipelines. However, strong and unique platform technologies still have the capability to attract lucrative deals, and firms at the discovery stage can gain from major alliances. Moreover, as high-value late-stage licensing products become more expensive, an alternative for pharmaceutical companies is to form alliances with emerging biotechnology firms with great potential, to gain access to proprietary technology platforms, drug targets and early-stage drug candidates (Belsey and Pavlou, 2005).

1.6 The Purpose of this Analysis

This study examines the central nervous system (CNS) drug industry by an assessment of industry attractiveness and identification of key success factors. The study further analyzes the deals and alliances transacted in the area of CNS disorders, at different stages of drug development and for different indications. The deals are assessed based on their structure and suggestions are made on what a small biotechnology company needs to do to attract similar alliance agreements from a potential partner.

2 ANALYSIS OF THE GLOBAL CNS INDUSTRY

In this chapter a background to the CNS therapeutic field is provided. The field is then analysed using Porter's Five Forces to determine how attractive it is from the perspective of a small innovative firm. However attractive a field is within an industry, firms still have to operate within the Key Success Factors (KSFs). The following section determines what these KSFs are.

2.1 Background

The global CNS drugs market was estimated at \$87 billion in 2004, with an annual growth rate of 9% (IMS World Review, 2005). The main therapeutic segments incorporated in this estimation included antidepressants (23% of sales), pain medication (18% of sales), antipsychotics (16% of sales), anti-epileptics (13% of sales), anti-migraine drugs (4% of sales), Alzheimer's disease medication (4% of sales), and Parkinson's disease therapies (3% of sales). Depression, followed by pain, constituted the largest CNS market segments in 2004. Datamonitor (2002) reported that an increasing number of companies are entering the CNS therapeutic areas associated with ageing, for example Alzheimer's disease and Parkinson's disease, given that the percentage of elderly people in western countries is expected to increase rapidly for the next ten years. These diseases will continue to be important candidates for better drugs and treatment approaches. As the prevalence of diseases associated with ageing continues to rise, there will be an increase in the demand for drugs, not only to manage them but also to take care of conditions that happen to occur at the same time, for instance depression and psychosis.

There are numerous firms participating in the global CNS industry, and the competition focuses on several disorders. Most of these diseases have unmet medical needs, mainly due to inadequate knowledge of the complex neurological system and its constituents. As a result, there

is an opportunity for increased R&D, more competition and more effective and safer medications for these diseases. The key competitive factor for companies developing new drugs is that their new products must be more effective and safer than existing therapies. This requires extensive R&D investment. Therefore, it is no accident that the companies that lead in the number of CNS drugs on the market are some of the key players in the pharmaceutical industry, such as Pfizer and Merck. These companies have huge R&D budgets and they are pursuing CNS disorders as a key research component. The second competitive factor is access to global marketing and distribution of products. Although the United States is still the biggest pharmaceutical market, Europe and Japan are big and expanding. The majority of the big pharmaceutical companies have extensive global production, marketing and distribution channels with which to compete in international markets. The key players in the global CNS industry include the large pharmaceutical companies such as Abbott Laboratories, AstraZeneca, Biogen Idec, Boehringer Ingelheim, Bristol-Myers Squibb, Eisai, GlaxoSmithKline, Johnson & Johnson, Merck & Co., Novartis, Pfizer, Roche, Sanofi-Aventis, Schering AG, Schering-Plough and Serono (Kalorama, 2005).

Although big pharmaceutical companies lead in the number of CNS drugs on the market, the future leaders in innovative CNS drug development are likely to emerge from the increasing number of small to medium size biotechnology firms with strong research ties to universities. In general, big pharmaceutical companies are disinclined to finance very early stage unproven technology due to the high risks involved. Instead, they are more likely to invest in small biotechnology companies with products in mid- to late-stage clinical development to minimize the risks of development and approval failure. According to Kalorama (2002), there is a level of acceptable risk depending on the market size and familiarity with the technology. For a larger market opportunity or a more familiar technology, big pharmaceutical companies may accept a higher risk and invest in early-stage compounds. However, many of the CNS market segments are

not very large and new technologies will be required to address these diseases. Therefore, to attract big pharmaceutical alliance partners, small biotechnology companies with new CNS drug candidates will need to demonstrate their potential and advance them in development to minimize risk.

Many big pharmaceutical companies currently under pressure to add new drug candidates to their dwindling product pipelines may ease these conditions. However, it is worth noting that the big pharmaceutical companies are seeking new products that they can take to the market fast, and CNS drugs present high risk opportunities with long development time. So there will have to be a balance between the need to fill product pipelines and the willingness to invest in higher risk early-stage CNS drug candidates.

According to DiMasi *et al.* (2004), the CNS drug industry exhibits the highest annual sales following product launch in comparison to the cardiovascular and anti-infective therapeutic categories. For example, the average annual sales for CNS drugs increase from approximately \$100 million to \$800 million from the first to the ninth year of marketing. Over the same period, the average annual sales for cardiovascular drugs grow from about \$100 million to \$700 million, while the annual sales for anti-infective therapeutics increase from approximately \$100 million to \$400 million.

Despite the high potential sales revenues, the CNS drug industry faces great challenges, for instance long clinical development and approval time, decreasing approval success rates, increasing regulatory hurdles and declining productivity (Gallen, 2004). CNS drugs have the longest clinical development and approval time of any therapeutic category. Clinical development and approval for CNS drugs takes an average of 12.6 years, in comparison to approximately 10.2 years for cancer drugs and about 6.3 years for cardiovascular therapeutics (Tufts CSDD, 2005). This could be attributed to the fact that CNS disorders are relatively rare in comparison to other

therapeutic classes, and it takes time to accumulate an adequate number of clinical trial patients to provide statistical significance. In addition, many CNS disorders, for instance multiple sclerosis, are characterized by unclear clinical endpoints, relapses and remissions, which lengthen the duration of clinical trials.

Approval success rates are low and they have been declining across all therapeutic categories. However, the success rates vary by drug category. For example, in a study of 671 drug candidates that had been approved for marketing in the United States by 1999, CNS drugs had an average approval success rate of 23%, compared to 33.1% for anti-infectives and 20.4% for cardiovascular therapeutics (DiMasi, 2001).

There has been a decrease in the output of new drugs, including CNS therapeutics, from 2000 to 2005. This decline could be attributed to three main factors, namely increased R&D cost and complexity, R&D inefficiency and poor R&D strategy (Tufts CSDD, 2005). In addition, clinical trial costs have been on the rise for six major reasons. First, it is difficult to conduct clinical trials for chronic and complex indications such as many CNS disorders. Second, there has been an increase in clinical trial size to achieve greater statistical significance for efficacy and safety. Third, there have been problems with patient recruitment and retention, due to relatively rare CNS disorders as well as adverse drug reactions. Fourth, increasing regulatory demands have raised the cost of meeting the requirements. Fifth, increasing market-oriented clinical trials targeting niche patient populations have made clinical trials even more complex and costly. Sixth, because of late-stage attrition, the high costs of clinical trials may not be recovered (Tufts CSDD, 2005). Consequently, the future growth of the CNS drug market is likely to be influenced more by the increasing proportion of the ageing population and resulting increase in total market size, rather than the introduction of new products (Kalorama, 2002).

2.2 Porter's Five Forces Analysis of the Global CNS Industry

Porter (1979) developed a model for analyzing the competitive forces that industries face in their markets, and hence providing an estimate of industry attractiveness. The main competitive forces identified by Porter are rivalry, threat of entry, threat of potential substitutes, power of buyers and power of suppliers. This framework is used to analyse the competitive environment of the global CNS industry and, as detailed throughout this section, indicates that the industry is of medium-high attractiveness overall.

2.2.1 Low Rivalry

The global CNS industry consists of numerous firms competing for financing to sustain their research, development and overall operations. In addition, the CNS industry experiences competition among companies targeting the same diseases, with each firm racing to be the first to get the drug on the market. Moreover, there is competition for alliances and collaborations with other companies. These partnerships provide financing, regulatory, manufacturing and commercialization expertise. As a result, there is competition for deals among biotechnology and pharmaceutical companies to take advantage of existing competencies and synergies.

The CNS industry growth rate of 9% (IMS World Review, 2005) is expected to increase rapidly with an increasing proportion of the ageing population in western countries. Rivalry is usually highest when there is slow growth and low demand, and firms compete intensely to gain market share. However, most CNS disorders have unmet medical needs, and as a result there is high demand for better therapeutics and an opportunity for increased R&D. Companies in the CNS industry have differentiated strategies, patents and semi-exclusivity based on the numerous disorders in this therapeutic category. The fast growth in the CNS market and the broad opportunities for R&D reduces competition among companies. Therefore, CNS drug companies

are less concerned about market share, and they are more focussed on developing new drugs that are more effective and safer than existing therapies.

The main customers in the CNS drug industry are the physicians who prescribe medications to their patients. In general, there are low switching costs in this industry. Given that the physicians' main interest is to provide their patients with the most effective treatment available, they have no problem switching from one product to another if it is likely to have added patient health benefits. However, marketing and distribution arms of large pharmaceutical companies are heavily focused on attracting and retaining physicians as their clients.

Fixed costs in the CNS industry are rather high because of expensive facilities and equipment for R&D and manufacturing. However, R&D and manufacturing may sometimes be outsourced to take advantage of existing competencies. Given that the CNS drug market is currently dominated by a few big pharmaceutical companies, and there is a wide range of product opportunities, fast growth of the industry and low switching costs, the overall rating for rivalry is low.

2.2.2 Medium Threat of New Entrants

2.2.2.1 Economies of Scale

The majority of CNS drug companies are mainly involved in R&D, pre-clinical and clinical trials. At these three stages, economies of scale do not apply. It is only after regulatory approval that economies of scale may be achieved in manufacturing, purchasing and commercialization. Most small to medium size biotechnology firms in the CNS industry are not able to take drugs to the market on their own. Their strategy is to take their drug candidates up to clinical trials, and then they seek alliances with big pharmaceutical companies to provide financing, regulatory, manufacturing and commercialization expertise. Therefore, economies of scale alone cannot deter new entrants from the CNS industry, since they do not have intentions of

pursuing manufacturing and commercialization on their own. However, unless a biotechnology firm is successful in establishing an alliance with a larger company, economies of scale will prevent it from competitive production of its drug.

2.2.2.2 Capital Requirements

The high costs of R&D and regulatory approval constitute a major obstacle to companies entering the CNS drug industry. It costs approximately \$800 million to develop and take a new drug through regulatory approval to the market (DiMasi *et al.*, 2003). Firms must constantly pursue and obtain reliable funding in order to survive. Therefore, high capital requirements would deter many small biotechnology companies from entering the CNS drug industry.

2.2.2.3 Access to Distribution Channels

Numerous biotechnology companies in the CNS industry do not have access to distribution channels. As a result, they seek alliances with big pharmaceutical companies for manufacturing and distribution of their products. Access to distribution channels, therefore, does not deter new entrants to the CNS drug industry. However, it may cause early exit of those firms unable to establish alliance partnerships.

2.2.2.4 Legislation or Government Action

The CNS drug industry is heavily regulated by government legislation in order to provide safe and effective medicines to patients. The regulatory bodies are the Food and Drug Administration (FDA) in the United States, and Health Canada in Canada. Other legal restraints include patent protection of compounds, technologies and drugs. Any new entrants must be prepared to comply with the regulations. Existing patents may act as a deterrent to entry for some firms.

2.2.2.5 Differentiation

The CNS drug industry targets several disorders with unmet medical needs. For firms competing on the same disorder, it may be important to achieve first-mover advantage by being the first to take a drug to the market. This may enable them to establish customer loyalty, and good relationships with insurance and health care organizations. However, the companies that follow may learn from the weaknesses of the first mover, for instance the side effects of their drugs, and develop a better product. The key competitive factor for companies developing drugs is that their new products must be more effective and safer than existing therapies.

The overall rating for the threat of new entrants into the global CNS drugs industry is medium, taking into account the factors that influence this force.

2.2.3 Medium Threat of Substitutes

Cheaper alternatives such as herbs, vitamins, minerals and yoga are available for many of the CNS drugs. However, these alternatives often have lower efficacy. In some cases, consumers may choose to purchase the cheaper substitute. Patent protection, effective for twenty years minus the clinical development and approval duration, may safeguard a firm from substitute products for a period of time. However, there is risk of infringement of patents, which may allow substitutes into the market. Moreover, following patent expiration, generic alternatives quickly erode the market share. The overall rating for potential substitute products as a threat to the global CNS drugs industry is medium, taking into account the factors that influence this force.

2.2.4 Medium Bargaining Power of Suppliers

The bargaining power of suppliers will influence their ability to restrict the freedom of a firm and affect its profitability. The key suppliers in the CNS drug industry include other firms, human resources and capital. In the CNS industry, the supply of talented human resources is relatively low, and the companies pursue treatments for several different disorders. R&D

constitutes a major component of a biotechnology firm's business, and the very specialized CNS research is in short supply of the highly skilled human resources required. This suggests a medium power of suppliers. Conversely, the large number of supplier firms who provide raw materials and the ease with which they can enter the industry may indicate a low power of suppliers.

Financial markets constitute a major supplier to the CNS industry. Drug development companies require large amounts of financing for R&D, clinical trials, manufacturing and commercialization. However, there is very limited financing from angel and venture capital investors that firms have to compete for. The overall power of suppliers in the global CNS industry is medium, considering the factors that influence this force.

2.2.5 Medium Bargaining Power of Buyers

The main customers for CNS drugs include doctors, hospitals, pharmacies, patients, health care and insurance companies. Doctors and hospitals diagnose patients, determine the type of treatment and make drug prescriptions. Pharmacies prepare and dispense drugs, and also provide advice and basic information to patients. Health care and insurance companies approve medical expenditures. Hospitals have a high bargaining power due to the large volumes of drug purchases they make, and the low cost of switching suppliers. Also, health care and insurance companies have high buying power because they approve medical expenditures. Doctors and pharmacies buy relatively smaller quantities and they are less concerned about price. This decreases their bargaining power. In general, patients have low bargaining power. Those who have health insurance are more interested in getting the best therapy available, rather than price. On the other hand, those who are not covered by health insurance may be more inclined to seek less expensive alternatives. Overall, the bargaining power of buyers in the CNS drugs industry is medium.

2.2.6 Summary of Porter's Five Forces Analysis

The global CNS drug industry is growing rapidly, and is expected to continue to grow over the next ten years with the increasing proportion of the ageing population in western societies. Many of the CNS disorders have unmet medical needs, thus creating opportunities for increased R&D and competition to generate better drugs for these ailments. Competitive advantage will, therefore, depend on the development of safer and more effective treatments for these disorders.

Analysis of Porter's Five Forces indicates that the global CNS industry is of medium-high attractiveness. The overall rivalry in the CNS industry is low, mainly because the participating pharmaceutical and biotechnology firms have differentiated strategies, patents and semi-exclusivity based on the numerous disorders in this therapeutic category. The threat of entry is also medium. This is because the only significant barrier to entry for new companies is capital requirements. The threat of substitute products is medium. Consumers are seeking more effective drugs with fewer side effects, and in some cases there are cheaper alternatives. However, patents may protect a firm from substitute products for a period of time. The overall power of suppliers is medium. This is because the suppliers of human and financial capital are in short supply, whereas the number of firms who provide raw materials is large and they can enter the market easily. On the whole, the power of buyers is medium, given that the high bargaining power of hospitals is balanced with the low bargaining power of doctors, pharmacies and patients. The large industry size and growth rate, unmet medical needs, low rivalry and absence of significant barriers to entry, make the CNS industry particularly attractive to new firms.

2.3 Key Success Factors in the Global CNS Industry

Key success factors (KSFs) for biotechnology firms operating in the CNS industry are directly linked to strategic and business objectives. In the global CNS industry, the key success factors include R&D efficiency, access to capital, alliances, human resources and location.

2.3.1 R&D Efficiency

Because of the high cost and long duration of R&D, firms in the CNS industry need to have high R&D efficiency in order to be successful. Many biotechnology firms in the CNS industry depend on research institutions, such as universities and medical schools, for innovations and intellectual property. Continuous research is required to provide incremental improvements and to identify new drug candidates, technologies and applications. It is not surprising that robust biotechnology firms have scientific advisory boards composed of leading research scientists and continue to form links with research institutions globally. In addition to R&D efficiency, intellectual property protection through patents is crucial to success (Niosi, 2003).

2.3.2 Access to Capital

Biotechnology firms participating in the CNS industry need reliable financing to cover the high costs of R&D and clinical trials. Angel and venture capital are critical sources of financing for biotechnology companies. Without these, a firm's only chance of commercializing its CNS product depends on early-stage alliance with a larger biotechnology or pharmaceutical company. In addition to obtaining funding, an entrepreneurial environment within the firm is crucial both for success and to achieve additional financing. An entrepreneurial environment includes having business acumen and the willingness to take business risks to achieve profitability.

2.3.3 Alliance Formation and Management

Conception of novel ideas and development of innovative technologies and products requires expertise, financing and time. Many firms in the CNS industry enter into strategic alliances and collaborations to access resources, expertise, new drug candidates and in some cases to share the risk of drug development. For instance, small biotechnology firms form alliances with big pharmaceutical companies who provide funding for the clinical trials, in addition to regulatory and commercialization expertise. The big pharmaceutical companies in turn gain access to innovative technologies and new drug candidates to fill their product pipelines while diversifying their risk. Alliances also allow a firm to focus on its core competencies while outsourcing the other parts of the product development to its partners. In addition, alliances can enable a company to enter new markets. So the KSF is the ability to form the appropriate alliance and to manage it once formed as analysed in chapter 4.

2.3.4 Talent Management

The ability to attract, reward and retain key talent is of crucial importance to firms in the CNS industry. First, excellent leadership is crucial to provide vision and direction to the company. Second, good business management abilities are important in communicating with investors to secure the badly needed financing. Third, highly skilled scientific talent in the very specialized CNS area are in short supply, and many firms compete to recruit from the same small pool. In a biotechnology company, management skills play a greater role than the technology because of the long duration of clinical development and the complex regulatory approval process. Therefore, a biotechnology firm needs CNS scientific talent as well as managerial talent to develop and manage alliances. Location can play a significant role in the ability to attract and retain key talent.

2.3.5 Belonging to and Making the Most of Clusters

Geographic location of a firm may affect its growth and profitability. Many biotechnology firms are located in cluster areas near leading research institutions, mainly because the majority of the companies grew as spin-offs from these institutions. Close proximity to research institutions allow biotechnology firms to gain access to innovative technologies, drug candidates, human resources and intellectual property. A cluster attracts other firms including suppliers, venture capital, and legal and accounting service providers. A cluster also provides an available talent pool including top managers, employees and consultants experienced in the drug development industry. Firms in a region with a higher concentration of biotechnology companies usually have higher market valuation compared to those in regions with a lower concentration (Stuart and Sorenson, 2003). The close proximity of companies in a cluster also promotes collaboration, R&D efficiency and entrepreneurial attitude and allows spin-off development.

2.3.6 Summary of Key Success Factors

The key success factors for new firms are R&D efficiency, access to capital, alliances, human resources and location. New firms need innovative technologies and products to be successful. Financing is crucial for the costly R&D, clinical development and approval phases. Through strategic alliances, companies may gain access to expertise, resources, funding and new products. Skilled managerial and scientific talent is scarce in the CNS industry sector, and firms need to attract, reward and retain them. Firms located in cluster areas benefit from an available talent pool, suppliers, venture capital, access to leading research institutions and potential collaboration with other companies.

2.4 Industry Summary

The CNS therapeutic sector is a good area for a small biotechnology company, as there is still plenty of room for a lot of innovation, which big pharmaceutical companies need. The big pharmaceutical companies' need for innovation provides a readily available outlet for novel discoveries and allows small biotechnology companies to occupy the part of the value chain they are good at, namely innovation. However, to get value from this excellent science, small biotechnology firms need efficient R&D, top scientific and managerial talent, access to capital, an ability to form and manage alliances and to make the most of being small by locating within a cluster and gaining the maximum from it.

3 INTERNAL ANALYSIS OF A SMALL FIRM IN THE CNS INDUSTRY

3.1 General Analysis

This section analyses a small Canadian biotechnology firm participating in the CNS drug industry. This firm is referred to as Company X in this analysis. Based in Vancouver in British Columbia, the company is developing drugs that protect against CNS disorders such as Alzheimer's disease, mild cognitive impairment, traumatic brain injury, stroke, multiple sclerosis and neuropathy. Company X is listed on Toronto Stock Exchange (TSE).

3.1.1 Company Structure

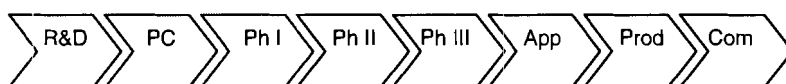
Founded in 2001, the company represents a typical small biotechnology firm with a staff of twelve people at the head office. The executive team consists of the Chairman, the President & Chief Executive Officer, the Co-founder & Chief Scientific Officer, the Advisor for Clinical Development & Regulatory Affairs, the Vice-President for Drug Development, the Vice-President for Clinical Operations and the Chief Financial Officer. In addition, there is a Director of Business Development and a Director of Corporate Development. The Board of Directors consists of seven members, and the Scientific Advisory Board is composed of ten leading scientists in CNS research. The R&D facilities are situated at a different location overseas.

3.1.2 Product Opportunities

The company's proprietary discovery platform has led to the development of a unique category of peptide compounds that have shown broad efficacy in many pre-clinical models of CNS disorders. Currently, the company has two clinical drug development programs. One is an intranasal formulation for Alzheimer's disease, and the other is an intravenous formulation for

mild cognitive impairment associated with cardiac artery bypass surgery. The product pipeline consists of two drug candidates in Phase I clinical trials, two in pre-clinical testing and one in R&D pre-target validation. Figure 1 shows the position of the company in the CNS drug development value chain.

Figure 1 CNS Industry Value Chain.



PC = Preclinical; Ph = Phase; App = Approval; Prod = Production; Com = Commercialization.

3.1.3 Company Strategy

The company does not have the capability or resources to develop its drug candidates and to take them to the market on its own. However, it has a portfolio of products that are appropriate for a partnership strategy because they are novel, proprietary and target large markets of unmet medical need. It is, therefore, seeking licensing, acquisition, co-development and partnering deals with value-added biotechnology and pharmaceutical companies. Specifically, the company is looking for complementary science or expertise relevant to its core strengths in CNS disorders, and the potentials for a good strategic fit.

3.1.4 Financing

The company has raised approximately CAD\$25 million in funding so far through venture capital investment and subsequent Initial Public Offering (IPO). At present it has about CAD\$12 million in the bank, which should last till the fourth quarter of 2007, and cover the two Phase II clinical trials which they are anticipating. The company is operating on a burn rate of about CAD\$500,000 per month, with the resources mainly focused on developing the compounds. The funds are spent 4-to-1 on R&D versus general and administrative expenses. The

company funds the research laboratory at an institution abroad. By having its shares listed on the Toronto Stock Exchange, the company has opened up to a broader category of investors, and it now has more people looking at its portfolio.

3.1.5 Key Success Factors

Key success factors were discussed in chapter 2 in relation to the strategic and business objectives of biotechnology firms operating in the CNS industry. R&D efficiency, access to capital, alliances, human resources and location were identified as the vital requirements.

Company X rates high in R&D efficiency. Its core competence in R&D efficiency has led to the development of a proprietary discovery platform that has generated a unique category of peptide compounds targeting major CNS disorders. The company's product pipeline consists of two drug candidates in Phase I clinical trials, two in pre-clinical testing and one in R&D pre-target validation. Company X has intellectual property protection through patents of its drug candidates. The company's Scientific Advisory Board is composed of ten leading scientists in CNS research. Company X collaborates with a leading university and a national research institution to access innovations and intellectual property.

Company X rates medium-low regarding access to capital. The company needs financing to cover the high costs of R&D and clinical development of its drug candidates. So far, Company X has raised approximately CAD\$25 million through venture capital investment and subsequent Initial Public Offering (IPO). Currently, it has about CAD\$12 million in the bank, which should last till the fourth quarter of 2007. The company is seeking alliances with a larger biotechnology or pharmaceutical company to provide financial support. Company X exhibits an entrepreneurial environment which is crucial both for success and to achieve additional financing. The CEO brings extensive business management experience and entrepreneurial spirit. The Board of Directors is a solid team comprised of biotechnology industry and business leaders.

Company X rates high as a potential alliance partner. It has a portfolio of products that would be attractive to big pharmaceutical and biotechnology companies because they are novel, proprietary and target large markets of unmet medical need. Its core competence is innovative CNS research, and it does not have the capability or resources to develop its drug candidates and to take them to the market on its own. The company is, therefore, seeking licensing, acquisition, co-development and partnering deals with value-added biotechnology and pharmaceutical companies. The ability to form the appropriate alliance and to manage it will be crucial for the company's success.

Regarding talent management, company X has a medium rating. A small biotechnology firm needs CNS scientific talent as well as managerial talent to develop and manage alliances. There is a shortage of top scientific and managerial talent in the CNS industry, especially outside the major North American biotechnology clusters. Therefore, many firms compete to recruit from the same small pool. Company X, being small in size, may not be able to provide financial rewards that larger firms offer to attract and retain top-tier employees.

Company X is located in the Vancouver biotechnology cluster, which has a medium-low rating. In comparison to major North American biotechnology clusters, such as the San Francisco Bay Area, the Vancouver cluster is relatively young. Its advantages include access to excellent basic life science research, relatively low costs of operations, good government incentives for research, angel financing for entrepreneurial companies, and a superior quality of life. However, the Vancouver cluster has an inadequate supply of local venture capital. It is also deficient in top scientific, managerial and regulatory talent in the CNS sector. Moreover, there is no big pharmaceutical company in this cluster. Firms located in major cluster areas benefit from an available talent pool, suppliers, venture capital, access to leading research institutions and potential collaboration with other companies.

3.2 SWOT Analysis

3.2.1 Strengths

The company's strengths lie in its core competence in CNS research. Its Scientific Advisory Board with leading scientific experts in CNS disorders reflects this. In addition, the company's unique and proprietary products are directed at large markets with unmet medical needs, and they could have a competitive advantage over current therapies for these disorders. The company has intellectual property patent protection for these compounds. In addition, the company has a visionary Chairman who has successfully founded and led two other biotechnology companies in the past. The CEO brings extensive business management experience and entrepreneurial spirit. The Board of Directors is a solid team comprised of biotechnology industry and business leaders.

3.2.2 Weaknesses

Despite its great science and innovative compounds, the company has no products on the market and no sales revenues. In addition, it has no manufacturing and commercialization capabilities so it will have to rely on other companies' expertise. There is a shortage of top talent in CNS scientific research and business leadership, especially outside the major North American biotechnology clusters, and being a small company, it may not be able to provide financial rewards that larger firms offer to attract and retain top-tier employees.

3.2.3 Opportunities

The company's innovative and proprietary products target large markets with unmet medical needs. The global CNS drug industry was estimated at \$87 billion in 2004, with an annual growth rate of 9% (IMS World Review, 2005). This growth rate is expected to increase rapidly over the next ten years with the increasing percentage of the ageing population in western societies. The company's unique class of compounds have shown efficacy in eight different

indications in CNS diseases. This may allow the company to develop a risk balanced drug portfolio.

3.2.4 Threats

The CNS drug industry is competitive and subject to ongoing technological change. Development by other firms may render Company X's drug candidates or technologies non-competitive. The market leaders in the CNS industry are big pharmaceutical companies who have greater R&D capabilities, as well as more manufacturing, marketing, financial and managerial resources. This creates significant competition. Moreover, CNS drugs have the longest clinical development and regulatory approval time compared to other therapeutic categories. The company has to be able to quickly adapt to possible changes in the regulations. The scarcity of financing for R&D and clinical development present a significant threat that the company has to address, as it still needs to secure funding for additional clinical development after Phase II.

3.3 Summary of Internal Analysis

This company's strength is above all that it has a number of potential drugs in a therapeutic area where medical needs are very much unmet in a growing market. It has no intention of occupying the entire value chain as it wishes to continue concentrating on innovation. With regards to KSFs it rates high in R&D efficiency as demonstrated by its innovative proprietary technology platform. Similarly, it rates high as a potential alliance partner because its portfolio of products would be attractive to big pharmaceutical and biotechnology companies who are hungry for innovation. However, the company has challenges in accessing capital and attracting, rewarding and retaining top CNS scientific and managerial talent, particularly because of its location in Vancouver, outside the major North American biotechnology clusters. The most important KSF is alliance formation and management. The next chapter analyzes these in detail.

4 ANALYSIS OF CNS DEALS

4.1 Overview

In this study, a total of nineteen pharmaceutical and biotechnology strategic alliance deals in the CNS area from 2000 to 2005 are analyzed. The average total payments, which include the exclusive rights to market drugs in specified geographic regions, were \$156.3 million for Phase I, \$233 million for Phase II and \$388 million for Phase III deals. The largest deal, between Biogen Idec and PDL BioPharma for multiple sclerosis, was worth a total of \$800 million.

Approximately 79% of the deals analyzed are for chronic indications, compared to only about 21% for acute indications. The average total deal size for chronic indications was \$261.9 million, compared to \$184.3 million for acute indications.

As discussed below, the factors that influenced deal size in this study include market size, first-in-class compounds, clinical trial data, number of compounds licensed, proprietary technology platform, freedom to operate, cost of treatment, third party endorsement, reprofiling, unproven treatment with high risk, advantages over current therapies, geographic restriction, chronic/acute indications and stage of development. In general, late-stage drug candidates attracted larger deals compared to early-stage compounds, while chronic indications were valued more than acute indications. Positive human efficacy data from clinical trials and advantages of the new medication over current therapies further contributed to larger deal sizes. Deals involving many compounds, many indications, or a proprietary technology platform, capable of generating additional products, tended to be more lucrative than those with only one compound or one indication. Also, drugs that were first-in-class compounds, received third party endorsement or targeted a big market size, generally commanded large deals. In addition, deals for diseases with

high treatment costs or where the licensee needed freedom to operate, tended to be worth more. Diseases whose treatments involve biologics generally attracted larger deals in comparison to those that are treated with new chemical entities (NCE), because of the higher cost of biologics. On the other hand, smaller deals were associated with geographic restrictions of exclusive rights, reprofiling and unproven treatment with high risk. In the following sections, the above mentioned factors are discussed using relevant examples of deals. The deals are segmented according to stage of development.

4.2 Phase I CNS Deals

The average total deal size for Phase I chronic indications (n=5) was \$183.4 million, while Phase I acute indications (n=2) had an average deal size of \$88.5 million. The largest Phase I deal, between Merck & Co. and DOV Pharmaceuticals for depression, was worth a total of \$455 million. On the other hand, the smallest Phase I deal, between NeuroSearch and Abbot Laboratories for the treatment of pain, totalled \$17 million. However, this deal could be much larger, given that the \$17 million payment applied to each successfully developed compound and all R&D costs were to be covered by Abbott. The factors that influenced the size of the Phase I deals analysed included market size, first in class compounds, clinical trial data, number of compounds licensed, proprietary technology platform and chronic/acute indications (Table 1).

Table 1 Factors Influencing the Size of Phase I CNS Deals

Factor	Source	Partner	Indication	Deal Size
Market size	DOV	Merck & Co.	Depression	455
	Acumen	Merck & Co.	Alzheimer's	96
Clinical trial data	Vernalis	Biogen Idec	Parkinson's	100
First-in-class compound	Memory	Roche	Alzheimer's	150
No of compounds	Memory	Roche	Alzheimer's	150
Technology platform	Neurogen	Merck & Co.	Pain	160

Deal size in US\$1,000, 000.

4.2.1 Market Size

According to the IMS World Review (2005), the global CNS drugs market was estimated at \$87 billion in 2004. The main therapeutic segments included were antidepressants (23% of sales), pain medication (18% of sales), antipsychotics (16% of sales), anti-epileptics (13% of sales), anti-migraine drugs (4% of sales), Alzheimer's disease medication (4% of sales), and Parkinson's disease therapies (3% of sales). Depression (23% of sales), followed by pain (18% of sales), constituted the largest CNS market segments in 2004. As discussed below, deals on indications with large market size were generally larger compared to those involving small market sizes.

4.2.1.1 Merck & Co. and DOV Pharmaceutical

Merck & Co. and DOV Pharmaceutical entered into an agreement on August 05, 2004 for the development and commercialization of DOV's novel triple uptake inhibitors, DOV 21,947 and DOV 216,303, for the treatment of depression and related psychiatric disorders. Merck licensed exclusive worldwide rights to DOV 21,947 for all therapeutic indications and to DOV 216,303 for the treatment of depression, anxiety and addiction. Merck committed to pay to DOV \$35 million upfront and milestone payments of \$120 million.

The total deal size was worth \$455 million. This deal was likely so large because depression is the largest therapeutic segment constituting 23% of sales within the worldwide CNS market of \$87 billion in 2004 (IMS World Review, 2005). Depression affects more than 50 million people worldwide annually. In addition, DOV's compounds have shown to be safe, well-tolerated and highly efficacious compared to commonly used antidepressants in early-stage clinical studies. Moreover, Merck licensed two compounds, DOV 21,947 and DOV 216,303. Lastly, DOV's novel triple uptake inhibitors that affect the neurotransmitters norepinephrine,

serotonin and dopamine have the potential to provide new options for the treatment of depression. Current therapies are faced with variable response or negative side effects.

4.2.1.2 Biogen Idec and Vernalis

Biogen Idec and Vernalis entered into an agreement on June 24, 2004 to advance research into Vernalis' adenosine A2A receptor antagonist program, which targets Parkinson's disease and is also investigating potential targets for new antidepressant drugs. Under the agreement, Biogen Idec received exclusive worldwide rights to develop and commercialize Vernalis' lead Phase I compound, V2006 for Parkinson's disease. In addition, the alliance gave Biogen Idec the right to develop one back-up compound to V2006 and option rights over Vernalis' A2A antagonist research program.

The total deal size was worth at least \$100 million. Biogen Idec agreed to make an immediate investment of \$6 million through subscription for ordinary shares, and to purchase an additional \$4 million in the event of a future Vernalis financing. In addition, Biogen Idec committed to pay Vernalis an initial license fee of \$10 million plus milestones payments, and royalties that were not disclosed. Vernalis was able to get such a good deal on the basis of a number of factors. First, although the primary indication is Parkinson's disease, there is a great upside potential for depression. Depression is the leading therapeutic segment comprising 23% of sales, while Parkinson's disease constitutes 3% of sales, within the worldwide CNS market of \$87 billion in 2004 (IMS World Review, 2005). Second, V2006 had been demonstrated to be effective in pre-clinical models of Parkinson's disease, and a total of five Phase I trials had been completed by Vernalis. Third, A2A receptor antagonists may possess advantages over conventional dopaminergic treatments for Parkinson's disease with fewer of the associated side effects such as nausea and dyskinesia.

4.2.1.3 Merck & Co. and Neurogen Corporation

Merck & Co. formed an exclusive worldwide alliance with Neurogen Corporation on December 1, 2003, to research, develop and commercialize novel drugs for the treatment of pain. These drugs act on the vanilloid receptor (VR1), a major integrator of pain signals in the nervous system. In addition to its effects on pain, VR1 may also play a role in urinary incontinence. The total deal size was \$160 million. Merck agreed to give Neurogen \$15 million upfront payment, \$15 million equity purchase, \$12 million for R&D and license maintenance, plus \$118 million milestone payments for research, development, approval and commercialization. Merck also accepted to pay royalties to Neurogen on net sales of products.

The deal was worth \$160 million. Pain therapeutics represent 18% of sales within the worldwide CNS market of \$87 billion in 2004 (IMS World Review 2005). In addition, VR1 drugs have the potential to provide a new treatment option for pain. Moreover, the VR1 drugs were being developed for more than one indication namely, pain and urinary incontinence. Also, Merck needs Neurogen's proprietary discovery platform to generate new products.

4.2.1.4 Merck & Co. and Acumen Pharmaceuticals

Merck & Co. and Acumen Pharmaceuticals entered into a research collaboration and license agreement to develop therapeutic drugs for Alzheimer's disease. Merck licensed monoclonal antibodies and vaccines based on the amyloid-derived diffusible ligands (ADDL) technology. Under the agreement, Acumen was to receive up to \$96 million. This included an upfront payment, research funding and milestone payments for the research, development and approval of the first antibody and vaccine products. In addition, Merck committed to pay Acumen royalties on the sale of products from the collaboration and milestones payments for the attainment of certain sales levels. The deal was worth \$96 million. Alzheimer's disease represents a big future market, given the growing percentage of the ageing population.

4.2.1.5 Abbott Laboratories and NeuroSearch

Abbott Laboratories and NeuroSearch entered into an agreement on January 06, 2000 to discover, develop and commercialize novel compounds, namely ABT-202 and ABT-894 that act on an important family of ion channels, for the treatment of pain. The agreement gave Abbott exclusive worldwide sales rights to compounds that are discovered through the collaboration. Abbott agreed to finance all research and development and to give NeuroSearch \$17 million in milestone payments for each successfully developed compound. In addition, Abbott committed to pay to NeuroSearch royalties on sales of compounds resulting from the collaboration. Given that the \$17 million milestone payment applied to each successfully developed compound, and all R&D costs were to be covered by Abbott, the total deal size could be much larger. However, given that pain therapeutics comprise 18% of sales within the worldwide CNS market of \$87 billion in 2004 (IMS World Review 2005), this was not a good deal for NeuroSearch because Abbott did not make a firm commitment. It is likely that Abbott Laboratories wanted to cover themselves in case of drug development failure, especially given that the two candidates ABT-202 and ABT-894 were pre-clinical compounds. It is worth noting that the development of ABT-202 was discontinued in 2003.

4.2.2 Clinical Trial Data

Drug candidates with positive human efficacy clinical trial data generally attracted larger deals in comparison to those without such supportive results. Positive clinical trial data is an indication of potential success of the drug. One of the major problems in drug development is the low success rates in development and regulatory approval.

4.2.2.1 Merck & Co. and DOV Pharmaceutical

As discussed above, the deal between Merck & Co. and DOV Pharmaceutical for the triple uptake inhibitors, DOV 21,947 and DOV 216,303, for the treatment of depression was

worth \$455 million. The first contributing factor to the big deal size was the large market size for depression. In addition, early-stage clinical studies results showed that DOV's compounds were safe, well-tolerated and highly efficacious compared to commonly used antidepressants.

4.2.2.2 Biogen Idec and Vernalis

The deal between Biogen Idec and Vernalis for the adenosine A2A receptor antagonist program, which targets Parkinson's disease and depression, has been described above. The total deal size was worth at least \$100 million. The first product, V2006 had been demonstrated to be effective in pre-clinical models of Parkinson's disease, and a total of five Phase I trials had been completed by Vernalis.

4.2.3 First-in-Class Compounds

The first drug candidate to be developed in a new promising category of compounds tended to attract a larger deal in comparison to "me too" products. This is mainly because first-in-class compounds may have potential advantages over current therapies. As a result they have the potential to provide new treatment options.

4.2.3.1 Roche and Memory Pharmaceuticals

Roche and Memory Pharmaceuticals entered into an agreement on July 30, 2002 to develop compounds in the field of PDE4 inhibitors, namely MEM1414, MEM1917, MEM3454 and MEM63908 for Alzheimer's disease and depression. In addition, Roche and Memory agreed to develop compounds within the same drug class for other indications, such as depression. According to the terms of the license, Memory was to receive from Roche up to \$150 million in payments. This included \$8 million upfront payment, \$7 million research funding over the initial 2 years, \$1.5 million reimbursement for payments to Contract Research Organizations for MEM1414, plus milestones up to \$133.5M.

The deal was worth \$150 million primarily because PDE4 inhibitors, if approved, would be first-in-class compounds for Alzheimer's disease when the deal was signed in 2002. Second, depression is the biggest therapeutic segment representing 23% of sales, while Alzheimer's comprises 4% of sales, within the worldwide CNS market of \$87 billion in 2004 (IMS World Review, 2005). Third, the agreement involved many compounds for more than one indication.

4.2.3.2 Merck & Co. and Neurogen Corporation

The deal between Merck and Neurogen for the vanilloid receptor (VR1) drugs for the treatment of pain has been described above. The total value of the deal was \$160 million. In addition to the large size of the pain market, VR1 drugs are first-in-class compounds with the potential to provide a new treatment option for pain.

4.2.4 Number of Compounds

Deals in which more than one compound were licenced tended to be valued more than those involving only one drug candidate. Having more compounds indicates higher potential revenues. It also suggests a risk balanced portfolio, given the low success rates in drug development and regulatory approval.

4.2.4.1 Merck & Co. and DOV Pharmaceutical

As discussed previously, the deal between Merck & Co. and DOV Pharmaceutical for the triple uptake inhibitors, DOV 21,947 and DOV 216,303, for the treatment of depression was worth \$455 million. The first two factors influencing this deal size were the large market size for depression and positive clinical data. In addition, the deal involved two compounds, DOV 21,947 and DOV 216,303.

4.2.4.2 Roche and Memory Pharmaceuticals

The deal between Roche and Memory Pharmaceuticals for the PDE4 inhibitors for Alzheimer's disease and depression was worth \$150 million, as described earlier. The first two factors influencing the deal size were the potential for first-in-class compounds and the large market size for depression. Also, the deal included four compounds, namely MEM1414, MEM1917, MEM3454 and MEM63908.

4.2.5 Proprietary Technology Platform

In general, access to a proprietary technology platform increased the size of deals. This is because of the potential for generation of additional products from the technology platform. As a result, it is an indication of higher potential revenues.

4.2.5.1 Lexicon Genetics and Bristol-Myers Squibb

Lexicon Genetics Inc. and Bristol-Myers Squibb formed an alliance on December 18, 2003 for drug discovery, development and commercialization in the CNS field. Although no specific compounds were mentioned, according to the agreement, the alliance would have exclusive access to future neuroscience discoveries from Lexicon's proprietary gene knockout technologies for drug development. Lexicon was already analyzing 5,000 genes using its proprietary technology platform to discover their physiological functions and pharmaceutical utility to develop drug target. The agreement gave Bristol-Myers Squibb the first option to assume full responsibility for clinical development and commercialization.

According to the terms of the alliance, Lexicon was to receive up to \$116 million in payments from Bristol-Myers Squibb. This included an upfront payment of \$36 million and \$80 million in research funding. In addition, Lexicon was to receive clinical and regulatory milestone payments plus royalties on sales for each novel drug target for which Bristol-Myers Squibb developed a drug. Lexicon was in a position to command such a deal mainly because of its

strong proprietary gene knockout technology platform with the potential to support multiple product opportunities. Moreover, the alliance would give Bristol-Myers Squibb exclusive access to discoveries from Lexicon's technology platform.

4.2.5.2 Merck & Co. and Neurogen Corporation

As described earlier, the deal between Merck and Neurogen for the vanilloid receptor (VR1) drugs for the treatment of pain was \$160 million. The size of this deal was influenced by the large size of the pain market and the fact that VR1 drugs are first-in-class compounds. Also, Merck needs Neurogen's proprietary discovery platform to generate new products.

4.2.6 Chronic versus Acute Indications

In general, chronic CNS indications have longer clinical trials and the therapeutic end-points are not clearly defined. Examples are Alzheimer's disease, Parkinson's disease, multiple sclerosis, schizophrenia and depression. On the other hand acute CNS indications, such as pain and stroke, tend to have relatively shorter clinical trials and the clinical end-points are clearly defined. Out of the Phase I deals analysed, the two that involved acute indications were between Merck and Neurogen as well as Abbott and NeuroSearch, both for pain treatment. The rest of the Phase I deals were for chronic indications. The average total deal size for Phase I chronic indications (n=5) was \$183.4 million, while Phase I acute indications (n=2) had an average deal size of \$88.5 million.

4.3 Phase II CNS Deals

The average total deal size for Phase II chronic indications (n=6) was \$245.2 million, while the one Phase II acute indication had a deal size of \$160 million. The largest Phase II deal, between Biogen Idec and PDL BioPharma for multiple sclerosis, was worth a total of \$800 million. On the other hand, the smallest Phase II deal, between Titan Pharmaceuticals and

Schering AG for Parkinson’s disease, totalled \$26 million. The factors that influenced the size of the Phase II deals analyzed included freedom to operate, cost of treatment, clinical trial data, third party endorsement, proprietary technology platform, market size, reprofiling and unproven treatment with high risk (Table 2).

Table 2 Factors Influencing the Size of Phase II CNS Deals

Factor	Source	Partner	Indication	Deal Size
Freedom to operate	PDL	Biogen Idec	Multiple sclerosis	800
	Pozen	GlaxoSmithKline	Migraine	160
Cost of treatment	PDL	Biogen Idec	Multiple sclerosis	800
No of compounds	PDL	Biogen Idec	Multiple sclerosis	800
Clinical trial data	Targacept	AstraZeneca	Alzheimer’s	300
Third party endorsement	Targacept	AstraZeneca	Alzheimer’s	300
Technology platform	Targacept	AstraZeneca	Alzheimer’s	300
Market size	NeuroSearch	GlaxoSmithKline	Depression	221
	NeuroSearch	Boehringer Ingelheim	Alzheimer’s, Parkinson’s	80
Reprofiling	Merck KGaA	Genaisance	Depression	44.1
Unproven treatment	Titan	Schering AG	Parkinson’s	26

Deal size in US\$1,000, 000.

4.3.1 Freedom to Operate

Freedom to operate ensures that a company’s use of a technology or process does not infringe the intellectual property rights of others. Some approaches for obtaining freedom to operate include purchase of patents, in-licensing or cross-licensing. In this study, companies were willing to pay more to obtain freedom to operate for technologies that were vital for progress in their drug development programs.

4.3.1.1 Biogen Idec and PDL

Biogen Idec and PDL formed a collaboration on August 03, 2005 for the joint development, manufacture and commercialization of three Phase II antibody products. The agreement included daclizumab (Zenapax) for multiple sclerosis, M200 (volociximab) for renal cell carcinoma and HuZAFTM (fontolizumab) for Crohn's disease. Biogen Idec committed to make an upfront payment of \$40 million to PDL, and to purchase \$100 million of common stock from PDL. In addition, Biogen Idec committed to give \$660 million milestone payments of to PDL.

The deal was worth \$800 million, which is unusually large. This could be attributed to three main reasons. First, PDL is a leader in the development of humanized antibodies, and it owns the freedom to operate. Biogen Idec was probably willing to pay so much to have the freedom to operate to be able to use PDL's technology to humanize its antibodies. Second, in the multiple sclerosis market the cost of treatment is \$16,000 annually per patient, because biologics are used for medication. Third, the deal involved three novel Phase II antibody products, namely Zenapax for multiple sclerosis, M200 for renal cell carcinoma and HuZAFTM for Crohn's disease.

4.3.1.2 GlaxoSmithKline and Pozen

GlaxoSmithKline (GSK) and Pozen signed an agreement on June 12, 2003 for the development and commercialization of proprietary combinations of a triptan (5-HT_{1B/1D} agonist) and a long-acting non-steroidal anti-inflammatory drug (NSAID) for acute treatment and sustained pain relief of migraine headaches. The combinations covered by the agreement are referred to as MT 400. The agreement gave GSK exclusive rights in the United States to commercialize all therapies which combine either of GSK's currently marketed triptans with a long-acting NSAID. Pozen will be responsible for development, while GSK will provide formulation development and manufacturing. Under the agreement, GSK committed to pay to

Pozen an upfront fee of \$25 million and milestone payments of \$55 million relating to development, regulatory submissions and approvals. GSK also agreed to pay Pozen royalties on sales and sales performance milestones of up to \$80 million.

The deal was worth a total of \$160 million. Pozen owns the intellectual property rights for the combination and GSK needs the freedom to operate. GSK owns the triptans but without Pozen, it cannot use the combination. In addition, in Phase II clinical trial involving 972 patients, MT 400, using a marketed triptan and an NSAID, provided greater than 50% improvement for sustained pain relief over triptan monotherapy.

4.3.2 Cost of Treatment

High cost of disease treatment tended to increase the deal size in this study. Treatments based on biologic products, such as monoclonal antibodies, are generally more expensive than those involving new chemical entities (NCE). Diseases whose treatments involve biologics generally attracted larger deals in comparison to those that are treated with NCE's.

4.3.2.1 Biogen Idec and PDL

As described above, the deal between Biogen Idec and PDL for the three Phase II antibody products namely, Zenapax for multiple sclerosis, M200 for renal cell carcinoma and HuZAFTM for Crohn's disease, was worth \$800 million. The main factor influencing this deal was freedom to operate. In addition, the cost of treatment in the multiple sclerosis market is \$16,000 annually per patient, because biologics are used for medication.

4.3.3 Market Size

In general, the bigger the market size the larger the deal size. This is because bigger markets promise higher revenues. As discussed below, the size of certain deals were also

influenced by future market size, for instance deals on drugs targeting the increasing ageing population.

4.3.3.1 NeuroSearch and GlaxoSmithKline

NeuroSearch and GlaxoSmithKline formed a five-year research and development alliance on December 19, 2003. The alliance comprised research on ion channels and the treatment of CNS diseases including depression, anxiety, and schizophrenia. The option agreement gave GSK access to new drug candidates including the Phase II triple monoamine re-uptake inhibitor NS2359 and several other research programmes. According to the agreement, GlaxoSmithKline was to pay to NeuroSearch an upfront payment of \$46.8 million, plus research funding and milestone payments. In addition NeuroSearch was to receive royalties on sales of successfully launched compounds.

The deal was worth a total of \$221 million. Depression is the largest therapeutic segment constituting 23% of sales within the worldwide CNS market of \$87 billion in 2004 (IMS World Review 2005). Current antidepressants on the market are faced with variable response or negative side effects. Also, NS2359 affects the three neurotransmitters serotonin, noradrenaline and dopamine, and is expected to produce an optimal reduction in all symptoms of depression, and also has the potential to provide new options for the treatment of this disease.

4.3.3.2 NeuroSearch and Boehringer Ingelheim

NeuroSearch and Boehringer Ingelheim signed an agreement on February 08, 2002 for the development and marketing of NS2330 for the treatment of Alzheimer's disease and Parkinson's disease. Under the agreement, Boehringer was to pay to NeuroSearch \$20 million upfront and the remaining \$60 million would be payable in the period prior to marketing approval. Moreover, Boehringer was to pay to NeuroSearch royalties on sales of the drug. The agreement with Boehringer Ingelheim covered the whole world except for

the Nordic and Baltic countries, where NeuroSearch retained all rights to market NS2330. Note, however, that Boehringer Ingelheim terminated the development of NS2330 for Alzheimer's disease in 2005, because the results from three completed Phase II clinical studies in Alzheimer's and Parkinson's diseases did not meet the company's efficacy criteria to proceed with Phase III clinical development. Boehringer Ingelheim decided to terminate the development in the Alzheimer indication, while remaining options for Parkinson's disease are still being assessed.

The deal was worth \$80 million pre-marketing. Alzheimer's disease and Parkinson's disease are attractive to pharmaceutical companies because of the significant future market potential as a result of the increasing proportion of the ageing population. In addition, the initial Phase IIa clinical study in Alzheimer's disease patients yielded positive results in the form of a significant improvement of the most important components of the memory function, including the ability to pay attention, to store and recall information and the speed of access of items held in memory. Moreover, NeuroSearch's NS2330 compound has a unique mode of action and enhances the function of acetylcholine, noradrenaline and dopamine, all of which are impaired in Alzheimer's patients.

4.3.4 Clinical Trial Data

As discussed above, clinical trial efficacy data positively influenced the size of deals. These results gave the licensees more confidence in the compounds. Drug development and regulatory approval processes are faced with high risks of failure.

4.3.4.1 Targacept and AstraZeneca

Targacept and AstraZeneca formed an exclusive worldwide license and research collaboration agreement on December 31st, 2005 for the development and commercialization of Targacept's proprietary compound TC-1734 for the treatment of Alzheimer's disease, cognitive deficits in schizophrenia and other cognitive disorders. AstraZeneca committed to pay to

Targacept \$10 million upfront, \$26 million research funding and \$20 million at the beginning of a Phase II study on Alzheimer's disease. In addition, Targacept would receive royalties on sales.

The deal was worth \$300 million. Targacept had positive preliminary efficacy data on TC-1734. Moreover, there was also third party endorsement. TC-1734 was one of the two compounds chosen by the Treatment Units for Research on Neurocognition and Schizophrenia (TURNNS) to be evaluated for a neurocognition in schizophrenia trial in 2004. Furthermore, the agreement included the use of Targacept's proprietary drug discovery technology known as Pentad to discover additional compounds for AstraZeneca. This deal is backend loaded with a small upfront payment. This is not surprising because the market for schizophrenia is small.

4.3.4.2 GlaxoSmithKline and Pozen

The deal between GlaxoSmithKline (GSK) and Pozen for the combinations of a triptan and an NSAID for migraine headaches was worth a total of \$160 million. First, GSK needed the freedom to operate. Second, Pozen had positive efficacy data for MT400. In Phase II clinical trial involving 972 patients, MT 400, using a marketed triptan and an NSAID, provided greater than 50% improvement for sustained pain relief over triptan monotherapy.

4.3.5 Third Party Endorsement

Third party endorsement of a compound tended to add value to a deal. Validation by an independent body or institution gave the licensee more confidence with the compound. Because of the high costs and risks involved such supporting information is very important in deal negotiation.

4.3.5.1 Targacept and AstraZeneca

The deal between Targacept and AstraZeneca for TC-1734 for the treatment of Alzheimer's disease and schizophrenia was worth \$300 million, as previously described. Targacept had positive preliminary efficacy data on TC-1734. Moreover, there was also third

party endorsement. TC-1734 was one of the two compounds chosen by the Treatment Units for Research on Neurocognition and Schizophrenia (TURNs) to be evaluated for neurocognition in schizophrenia trial in 2004.

4.3.6 Number of Compounds

In general, the more compounds in a deal the higher the value of the deal. More than one compound in a deal provides a guarantee against product failure. Moreover, having many drug candidates is an indication of higher potential revenues.

4.3.6.1 Biogen Idec and PDL

The deal between Biogen Idec and PDL for the three Phase II antibody products namely, Zenapax, M200 and HuZAFTM was worth \$800 million, as described earlier. The deal size was influenced by Biogen Idec's need of the freedom to operate as well as the high cost of treatment of multiple sclerosis. Furthermore, the deal involved more than one compound.

4.3.7 Proprietary Technology Platform

The need for proprietary technology platforms generally increased the size of deals. A technology platform would allow the partner to develop additional drug candidates. Therefore, it could enhance future revenues.

4.3.7.1 Targacept and AstraZeneca

As discussed above, the deal between Targacept and AstraZeneca for TC-1734 for the treatment of Alzheimer's disease and schizophrenia was worth \$300 million. In addition to Targacept's positive clinical data and third party endorsement of TC-1734, the agreement included the use of Targacept's proprietary drug discovery technology known as Pentad to discover additional compounds for AstraZeneca.

4.3.8 Reprofiting

Reprofiting refers to identification of new indications for existing drug compounds.

When a failed drug is reprofiled for a different indication the deal value tends to be lower. This is because the licensor cannot continue with the development of the compound anymore, and is therefore willing to accept lower offers.

4.3.8.1 Genaissance Pharmaceuticals and Merck KGaA

Genaissance Pharmaceuticals acquired an exclusive worldwide license from Merck KGaA on September 23, 2004 to develop and commercialize vilazodone, a selective serotonin reuptake inhibitor (SSRI) and a 5HT_{1A} partial agonist for the treatment of depression. The total deal size was worth \$44.1 million, including a license fee and milestone payments. Merck retained an option to sell the drug or receive royalties if vilazodone is successful. This deal was small for an antidepressant because it is a typical case of reprofiling, which means identifying new uses for existing drugs. Merck had stopped developing vilazodone in 2003 after it failed to meet expectations in three studies involving 1,000 patients. Instead, Merck chose to focus its R&D resources on its main therapeutic areas of Oncology and CardioMetabolic Care. Genaissance intended to use pharmacogenomics to target vilazodone, aiming to identify biomarkers that make patients more likely to respond to the drug.

4.3.9 Unproven Treatment

In general, unproven treatments negatively influenced the size of the deals. This was more evident when high risks were involved in the treatment. Also, consumers may be concerned about adopting such treatments.

4.3.9.1 Titan Pharmaceuticals and Schering AG

Titan Pharmaceuticals established a corporate partnership with Schering AG on February 02, 2000 for the worldwide development, manufacture, and commercialization of Titan's novel cell therapy for the treatment of Parkinson's disease. The total deal size, including development funding and equity investment, was worth approximately \$26 million. In addition, Titan would receive funding for clinical trials and product royalties from Schering AG. Titan and Schering also agreed to mutually explore other potential therapeutic applications of Titan's cell-coated microcarrier (CCM) technology, under a one year exclusive option granted to Schering. The size of the deal is small for Parkinson's disease, and this may be attributed to concerns about cell therapy. This is an unproven treatment with high risk. Moreover, Schering is funding all clinical trials.

4.3.10 Chronic versus Acute Indications

Out of the Phase II deals analysed, the only one that involved an acute indication was between GlaxoSmithKline and Pozen for the treatment of migraine headaches. The rest of the Phase II deals were for chronic indications. The average total deal size for Phase II chronic indications (n=6) was \$245.2 million, while the one Phase II acute indication had a deal size of \$160 million.

4.4 Phase III CNS Deals

The average total deal size for Phase III chronic indications (n=4) was \$385 million, while the one Phase III acute indication had a deal size of \$400 million. The largest Phase III deal, between New River Pharmaceuticals and Shire Pharmaceuticals for ADHD, was worth a total of \$500 million. On the other hand, the smallest Phase III deal, between Merck and Lundbeck for sleep disorders, totalled \$270 million. The factors that influenced the size of the Phase III deals analyzed included advantages over current therapies, market size, clinical trial

data, first-in-class compound, late stage of development, geographic restriction of rights and proprietary technology platform (Table 3).

Table 3 Factors Influencing the Size of Phase III CNS Deals

Factor	Source	Partner	Indication	Deal Size
Advantages over current	New River	Shire	ADHD	500
	Organon	Pfizer	Schizophrenia	370
Technology platform	New River	Shire	ADHD	500
Market size	Pain Inc.	King Pharma	Pain	400
Clinical trial data	Neurocrine	Pfizer	Insomnia	400
First-in-class compound	Lundbeck	Merck & Co.	Sleep disorder	270
Geographic restriction	Lundbeck	Merck & Co.	Sleep disorder	270

Deal size in US\$1,000, 000.

4.4.1 Advantages over Current Therapies

In this study, drug candidates that exhibited significant advantages over current therapies were associated with large deal sizes. Such products had a better chance of getting regulatory approval. Also, these products would be adopted by consumers rather quickly to gain significant market share.

4.4.1.1 New River Pharmaceuticals and Shire Pharmaceutical Group

New River Pharmaceuticals and Shire Pharmaceutical Group signed an agreement on December 31, 2004 to enter into exclusive negotiations to complete a transaction relating to the commercialization of NRP104, New River's Phase III compound for treatment of Attention Deficit Hyperactivity Disorder (ADHD) in the United States. The agreement also included further product development for other potential indications on a worldwide basis. Under the agreement, Shire would pay to New River \$50 million upfront and \$450 million approval and sales milestone payments.

The deal was worth a total of \$500 million. New River was offering a late-stage Phase III compound, NRP104. Moreover, NRP104 presented a safer, abuse resistant and effective alternative to current amphetamine-based therapies used to treat ADHD. In addition, the deal provided development options for new compounds and other indications. For instance, under the agreement, New River would continue to develop several drug candidates, particularly NRP290, an opioid analgesic for the treatment of acute pain. Furthermore, the ADHD market is one of the most rapidly growing in the CNS area, and it is anticipated to continue growing as awareness of the condition increases.

4.4.1.2 Neurocrine and Pfizer

Neurocrine Biosciences and Pfizer entered into a global agreement on Dec. 19, 2002 for the exclusive worldwide development and commercialization of indiplon, Neurocrine's Phase III compound for the treatment of insomnia. Under the agreement, Pfizer committed to pay to Neurocrine \$100 million upfront payment and up to \$300 million in milestone payments. In addition, Neurocrine would receive from Pfizer additional funding for the ongoing development of indiplon and royalties on worldwide sales plus co-promotion fees in the United States. The companies agreed to collaborate on the clinical development of indiplon and to co-promote the product in the United States, while Pfizer would hold an exclusive license to develop and market indiplon outside the United States. Following the U.S. launch of indiplon, Pfizer pledged to grant Neurocrine a staged \$175 million secured short-term credit facility, indicating that the deal could be worth more.

The deal was worth a total of \$400 million. Neurocrine was providing a late-stage Phase III compound, indiplon. Second, indiplon exhibited positive results from the first Phase III clinical trial, achieving both primary and secondary endpoints of sleep initiation. Results demonstrated that Indiplon was safe, well tolerated, and effective in subjects with transient insomnia, achieving rapid sleep induction without next day residual effects. Third, indiplon addressed a large market

opportunity. Insomnia is a prevalent neurological disorder in the United States, with about one-half of the adult population reporting trouble sleeping a few nights per week or more, according to the National Sleep Foundation (NSF). Current therapies have problems, including the ability to maintain sleep throughout the night without next-day residual effects.

4.4.1.3 Pain Therapeutics and King Pharmaceuticals

Pain Therapeutics and King Pharmaceuticals entered into a strategic alliance on Nov. 10, 2005 to develop and commercialize Remoxy and other abuse-resistant opioid painkillers. Remoxy (long-acting oral oxycodone) is in Phase III clinical development by Pain Therapeutics for the treatment of moderate-to-severe pain. King committed to make an upfront payment of \$150 million and milestone payments of up to \$150 million based on the successful clinical and regulatory development of Remoxy and other abuse-resistant opioid products. King also took responsibility for all R&D expenses related to this alliance, which could total \$100 million.

The value of this alliance could exceed \$400 million, plus royalties. Pain medications comprise 18% of sales within the worldwide CNS market of \$87 billion in 2004 (IMS World Review 2005). In addition, Remoxy was proven to be a safe and abuse-resistant opioid painkiller, in comparison to some of the other current opioid painkillers. Moreover, Remoxy's technology platform foundation could be applied to develop a pipeline of other abuse-resistant opioid painkillers. Furthermore, the drug Remoxy was in late-stage Phase III clinical development.

4.4.2 Market Size

As mentioned previously, market size positively influences deal size. Bigger markets promise higher potential revenues. Hence licensees are willing to pay more for deals on drugs targeting large disease populations.

4.4.2.1 Pain Therapeutics and King Pharmaceuticals

The deal between Pain Therapeutics and King Pharmaceuticals for Remoxy and other abuse-resistant opioid painkillers was worth at least \$400 million, as mentioned above. In addition to Remoxy's advantages over current therapies, pain medications comprise 18% of sales within the worldwide CNS market of \$87 billion in 2004 (IMS World Review 2005).

4.4.2.2 New River Pharmaceuticals and Shire Pharmaceutical Group

As discussed previously, the deal between New River Pharmaceuticals and Shire Pharmaceutical Group for NRP104, New River's compound for treatment of ADHD, was worth a total of \$500 million. The future market size potential for ADHD is large. The ADHD market is one of the most rapidly growing in the CNS area, and it is anticipated to continue growing as awareness of the condition increases.

4.4.2.3 Neurocrine and Pfizer

The deal between Neurocrine Biosciences and Pfizer for indiplon, Neurocrine's compound for the treatment of insomnia, was worth a total of \$400 million. Indiplon addressed a large market opportunity. Insomnia is a prevalent neurological disorder in the United States, with about one-half of the adult population reporting trouble sleeping a few nights per week or more, according to the National Sleep Foundation (NSF).

4.4.2.4 Pfizer and Organon

Pfizer and Organon, the human pharmaceutical business unit of Akzo Nobel, entered into a global agreement on October 20, 2003 for the exclusive worldwide development and commercialization of Organon's Phase III compound, asenapine, a potential new psychotropic medication for the treatment schizophrenia and bipolar disorder. The companies agreed to collaborate on the clinical development and manufacturing of asenapine, and to co-promote the product in the United States, European Union, Japan and other markets. Under the agreement,

Pfizer would pay to Organon \$100 million upfront and up to \$270 million in regulatory and sales milestone payments.

The total deal size was worth \$370 million. Organon was offering a late-stage Phase III compound. Asenapine was well-tolerated and showed superior efficacy in Phase II clinical trials. In addition, schizophrenia drugs fall under the antipsychotics segment comprising 16% of sales within the worldwide CNS market of \$87 billion in 2004 (IMS World Review 2005). Moreover, asenapine is a 5HT₂/D₂ antagonist that belongs to a class of medicines known as atypical antipsychotics with a unique mechanism of action. These drugs act on both the 5HT₂ and D₂ receptors and show superior tolerability and efficacy compared to older antipsychotic medications that act mainly on D₂ receptors. Asenapine will, therefore, present additional options for patients and physicians in the management of psychoses. Psychotropic medications work for only about 70% of individual patients so new treatments are always needed.

4.4.3 Clinical Trial Data

Deal sizes tended to be higher when positive clinical trial data was available. These results reinforced the chances of success of a drug candidate. As a result the alliance partners would be willing to pay more.

4.4.3.1 Neurocrine and Pfizer

As mentioned earlier, the deal between Neurocrine Biosciences and Pfizer for indiplon, Neurocrine's compound for the treatment of insomnia, was worth a total of \$400 million. Indiplon exhibited positive results from the first Phase III clinical trial, achieving both primary and secondary endpoints of sleep initiation. Results demonstrated that Indiplon was safe, well tolerated, and effective in subjects with transient insomnia, achieving rapid sleep induction without next day residual effects.

4.4.3.2 Pfizer and Organon

The deal between Pfizer and Organon for asenapine, a new medication for schizophrenia and bipolar disorder, was worth \$370 million as described earlier. The potential market size for antipsychotics is large. Moreover, asenapine was well-tolerated and showed superior efficacy in Phase II clinical trials.

4.4.4 First-in-Class Compounds

The first drug to be developed in a new class of compounds presents new treatment options. This is particularly significant when the new category of drugs have advantages over conventional treatments. Consequently, they would be more attractive to potential licensees.

4.4.4.1 Merck and Lundbeck

Merck & Co and Lundbeck entered into an alliance on Feb 10, 2004 for the exclusive U.S. development and commercialization of gaboxadol, Lundbeck's Phase III compound for the treatment of sleep disorders. Merck committed to give Lundbeck an upfront payment of \$70 million and up to \$200 million in additional milestone payments. The two companies agreed to jointly complete the ongoing Phase III clinical program, with Merck funding the majority of the remaining development activities. The agreement provided for co-promotion of gaboxadol in the U.S. Also, Lundbeck would receive a share of gaboxadol sales in the U.S.

The total deal size was worth \$270 million. For a Phase III compound, this deal was relatively small compared to the others. Gaboxadol was a first in class compound, being a direct-acting GABA-A receptor agonist. Its novel mechanism of action was expected to yield a minimal risk of abuse, which might provide a competitive advantage over existing therapies in the market. In clinical trials, gaboxadol exhibited effective sleep-inducing as well as sleep-maintaining properties. Sleep disorders constituted only 4% of the global CNS market in 2004 (IMS World Review, 2005). The relatively small size of the deal could also be attributed to the fact that the

alliance had exclusive rights for commercialization of gaboxadol in the U.S. only, with the exclusion of other big markets, such as Europe and Japan.

4.4.5 Geographic Restriction of Rights

In some alliance agreements the licensor grants the licensee exclusive rights in certain countries only. This would limit the potential revenues from products sales. Hence, geographic restriction tends to lower the size of deals.

4.4.5.1 Merck and Lundbeck

The deal between Merck & Co and Lundbeck for gaboxadol, Lundbeck's compound for the treatment of sleep disorders, was worth \$270 million. This was relatively low for a Phase III deal. The alliance had exclusive rights for commercialization of gaboxadol in the U.S. only, leaving out other big markets, such as Europe and Japan.

4.4.6 Proprietary Technology Platform

As mentioned earlier, a proprietary technology platform provides the licensee with an opportunity to develop additional compounds. Therefore, it presents the potential of higher revenues. This tends to positively influence the deal size.

4.4.6.1 New River Pharmaceuticals and Shire Pharmaceutical Group

The deal between New River Pharmaceuticals and Shire Pharmaceutical Group for NRP104, for treatment of ADHD, was worth a total of \$500 million. The future market size potential for ADHD is large. Furthermore, Shire would benefit from the development of additional compounds from New River's technology platform.

4.4.6.2 Pain Therapeutics and King Pharmaceuticals

As discussed earlier, the deal between Pain Therapeutics and King Pharmaceuticals for Remoxy and other abuse-resistant opioid painkillers was worth at least \$400 million. The market size potential for pain is large. In addition, Remoxy's technology platform foundation could be applied to develop a pipeline of other abuse-resistant opioid painkillers.

4.5 Deals Summary

Biotechnology firms, such as Company X, and pharmaceutical companies operating in the global CNS industry need to form alliances for mutual benefit. Several factors influence the size of deals in these alliances. In this study, the stage of development was an important factor affecting deal size. In general, Phase III deals attracted the highest total payment, while Phase I deals received the lowest valuation. This is mainly attributed to the high risks of early-stage compounds in comparison to the lower risks of late-stage drug candidates. Moreover, the late-stage drug candidates had already given some indication from human clinical trials that they might be successful, and they were also closer to commercialization. Although late-stage deals were more lucrative, early-stage deals targeting large market opportunities also attracted large payments due to the high potential revenues. For example, the Phase I deal between Merck & Co. and DOV Pharmaceuticals for depression was worth a total of \$455 million (Table 1). Furthermore, the potential earnings from an early-stage deal could be huge, given that the licensee usually takes the greater share of the future sales revenues.

The availability of positive clinical trial data increased the value of the deals at all stages of development. These supportive data changed the risk profile of the drug candidates, suggesting a better chance of success in clinical development and approval. Also, first-in-class compounds commanded large deals, both in early-stage and late-stage development, because they had the potential to provide new treatment options. Moreover, first-in-class compounds with different

mechanisms of action might have different tolerability and safety profiles. Having more than one compound increased the deal value, both in Phase I and Phase II, because of higher potential revenues. It also reflected a risk balanced portfolio, given the low success rates in drug development and regulatory approval.

A proprietary technology platform was generally favourable to the deal size at all stages of development. This is because a technology platform provided the potential for generation of additional products. In general, chronic indications were associated with larger deals in comparison to acute indications. For chronic indications, the patients would take the medications for a long time; hence the products would generate higher revenues. However, an exception to this was the Phase III deal between Pain Therapeutics and King Pharmaceuticals for the painkiller Remoxy (Table 3). Although pain is an acute indication, this deal was worth \$400 million plus royalties because in addition to the large size of the pain market, Remoxy exhibited significant advantages over current therapies and its technology platform could be used to develop additional pain medications. Advantages over current methods significantly contributed to large deal sizes in Phase III, when the compounds had been proven through human clinical trials. Such products had a better chance of getting regulatory approval and market success.

In this study, companies were willing to pay more to obtain freedom to operate when they needed crucial technologies for their drug development programs. For example, the largest deal between Biogen Idec and PDL BioPharma for multiple sclerosis was worth a total of \$800 million (Table 2); Biogen needed freedom to operate to be able to use PDL's proprietary technology to humanize its antibodies. Deals on biologics tended to be valued more than NCE deals, due to the higher cost of the former. For instance, another contributing factor to the unusually large size of the deal between Biogen Idec and PDL BioPharma is that the treatment for multiple sclerosis involves a biologic product. Third party endorsement of a compound also

tended to add value to a deal, because validation by an independent body or institution gave the licensee more confidence in the compound.

Failed drugs that were subsequently reprofiled for different indications were associated with smaller deals, because the licensor could not continue with the development of the compound and was, therefore, willing to accept a lower offer. In general, unproven treatments negatively influenced the size of the deals. This was more apparent when high risks were involved in the treatment (Table 2). Geographic restriction of rights also tended to lower the size of deals. This could be attributed to the limited potential revenues from product sales in such alliances.

Taking into account the findings from this study, small biotechnology firms in the CNS industry need to advance their compounds in clinical development stage, obtain strong supportive human clinical trial data and target large market opportunities to attract good deals from potential partners. They also need to develop proprietary technology platforms capable of delivering a stream of innovative compounds, including first-in-class drug candidates to secure large deals. Furthermore, biotechnology firms need to develop compounds with significant advantages over current treatment methods, obtain third party endorsement and preferably target chronic indications to maximize value from alliance partners.

5 STRATEGIC ALTERNATIVES FOR COMPANY X

5.1 Identification of Alternatives

The main strengths of Company X include its core competence in scientific research in the CNS area, its proprietary discovery platform, its unique class of compounds targeting large markets of unmet medical needs and its patents for intellectual property protection. Its major weaknesses are lack of products on the market, and the absence of sales revenues. In addition, the company does not have the capability or resources to complete clinical development and undertake commercialization on its own. The current strategy of the company is to identify promising compounds for CNS disorders, develop them up to the end of Phase I clinical trials, and then look for partners. The current strategy mainly leverages the company's core competence in innovative scientific research. The first two drug candidates are currently in Phase I clinical trials. The strategic alternatives available to the company include licensing only (S1), licensing & co-development (S2), co-development only (S3), acquisition (S4) and full integration (S5). Table 4 summarizes the assessment of the four of these alternatives which are viable for Company X.

5.1.1 Licensing Only (S1)

The first strategic alternative for Company X is to maintain the current strategy of identifying novel compounds, developing them up to the end of Phase I clinical trials, and then seek partners for licensing. In a licensing deal the firm would grant another company the rights to use its intellectual property. The licensing deal terms typically include an upfront payment, milestone payments and royalties. The two partners need to have a strategic fit, for instance regarding expertise and therapeutic area.

This strategy will enable the company to generate revenues from the licensing deals to support its R&D. By out-licensing its compounds the firm will avoid the high costs and risks in drug development and regulatory approval, in which it has no expertise. This strategy will also allow the company to focus on its core competence in innovative research.

When a company out-licenses a product, it gives up the majority of the potential value of the product. For instance, in Phase I licensing 70-80% of the value goes to the partner, while in Phase III licensing the partner takes away 50% of the value (Brennan, 2006). Moreover, the royalty range for Phase I compounds is 6-10%, compared to 8-15% for Phase II and 10-20% for Phase III drug candidates (Edwards *et al.*, 2003). Therefore, by out-licensing its compounds in Phase I, the company will be giving away a significant portion of the value. Based on this study, Phase I deals are generally valued lower in comparison to later stage deals. Moreover, by continuing to focus on early-stage development the company will not be able to develop later-stage capabilities and assets. Furthermore, there is a risk that the licensee may fail to develop the product if they have their own compound, with an internal champion, for the same disease.

5.1.2 Licensing & Co-development (S2)

In a licensing & co-development arrangement, for instance if the company has two Phase I compounds, it could out-license one while retaining the other one for a co-development alliance. In this way, the company could benefit from the positive aspects of both licensing & co-development as described below, while spreading out the risks of drug development.

5.1.3 Co-development (S3)

In a co-development alliance the two partners jointly undertake defined aspects of the research, pre-clinical testing, clinical development, regulatory approval and commercialization. Usually the alliance is between a small biotechnology firm and a big pharmaceutical company. A successful co-development alliance requires strong managerial commitment, contractual

agreements and trust. For example, the Chairman of Company X has extensive management experience including founding and leading two other biotechnology companies. He also sits on the Board of Directors of several biotechnology companies. In addition, the CEO of Company X has extensive previous experience in managing several other companies.

In a co-development alliance, the firm would benefit from the financial resources, regulatory, manufacturing, sales and promotion expertise from the big pharmaceutical partner. Moreover, the risks of drug development and regulatory approval, as well as the profits from product sales would be shared, thus creating higher incentives for successful partnerships. Furthermore, a co-development alliance with a large partner would boost investor confidence in the firm. Overall, it will enable the firm to get its drugs to market.

Co-development partnerships often face managerial difficulties and co-ordination problems. This is mainly because the objectives of the partners may not be in alignment. In addition, the firm would be giving up a significant potential value of the product to the partner.

5.1.4 Acquisition (S4)

In an acquisition, the firm would be bought entirely by another company in exchange for cash or stock. This is a common exit strategy for small biotechnology companies, after they have added value through pre-clinical testing and clinical trials of their compounds. Acquisitions require a strategic fit between the two parties. The potential acquirer usually specializes in the same therapeutic area and needs complementary products or technologies, or it may want to buy out a competitor to improve its own strategic positioning.

In an acquisition the price is negotiated. Therefore, if the firm has a strategic value an acquirer may pay even more than the company is worth. Moreover, if multiple parties bid the price could be even better.

After the acquisition, the firm will lose control to the acquirer. The acquirer is likely to restructure the executive team and the organization structure. This means some of the key employees may not be retained by the acquirer. In addition, relationships with major suppliers and other stakeholders of the acquired company may be impaired because of change in leadership.

5.1.5 Full Integration (S5)

In full integration the company would do the entire clinical development and commercialization on its own. However, Company X does not have the financial resources, physical assets and key human resource talent required for full integration. Therefore, full integration is not a feasible alternative for the company at present.

5.2 Evaluation of Strategic Alternatives

For Company X to be successful in the CNS industry it needs to choose a strategic alternative that is in alignment with the goals of the firm, and that will also add value to shareholders' investments. To evaluate the strategic alternatives generated above, the goals of the company have been assumed to be short term cash flow, long term profitability, access to top talent, market share, control of the company, and portfolio synergy (Table 4). The choice of the criteria is explained below.

5.2.1 Short Term Cash Flow

As mentioned in chapter 3, Company X has only about CAD\$12 million in the bank at present, which should last till the fourth quarter of 2007. Moreover, the Vancouver biotechnology cluster has a short supply of local venture capital. Therefore, the company is in urgent need of cash to support its core competence in innovation. Short term cash flow is crucial for financing the costly R&D and early-stage clinical development. As discussed in chapter 2, access to capital

is a top KSF for a small biotechnology firm in the CNS industry. A licensing only deal would infuse a significant amount of cash into the company to support its R&D activities, and to generate additional compounds for future deals or commercial considerations. While an acquisition would bring the highest amount of payment, it would be a one time transaction and the company may not be the same again, given the new leadership. Co-development would generate the lowest short term cash flow given that it would be a long-term relationship and the responsibilities, risks and profits would be shared. In a licensing & co-development alliance the amount of short term cash injection will be lower compared to a licensing only deal because only a given portion of the compounds would be licensed.

5.2.2 Long Term Profitability

Company X needs a reliable source of financing to support its innovative research, and the Vancouver cluster has inadequate local venture capital. As mentioned in chapter 3, Company X is currently not profitable, with no products on the market generating revenues. Access to capital is a major KSF for small biotechnology companies, as described in chapter 2. Moreover, a major goal of the company is to add value to shareholders' investment. Therefore, long term profitability is critical for the continued innovation and success of the firm. The current company strategy of developing compounds for licensing deals, and using the payment to develop additional compounds, would produce medium level long term profitability. On the other hand, a co-development alliance would enable the company to use the financial resources, regulatory and commercialization expertise of a large pharmaceutical or biotechnology partner to get its products to the market, thus achieving high long term profitability. For an acquisition, the company would only benefit from a one time payment, and with the new management and restructuring there would be no certainty about long term profitability.

5.2.3 Access to Top Talent

As discussed in chapter 3, because of the small size of Company X and its location in Vancouver outside the major North American biotechnology clusters, it may not be able to access, attract and reward top scientific and managerial talent in the CNS sector. The ability to access top talent is crucial for success of firms in the CNS industry. A co-development alliance would enable a small firm to access the available top talent from its large pharmaceutical partner. Co-development alliances provide an opportunity for dissemination of knowledge and tacit information between the partners. On the other hand, a deal involving licensing only will provide the lowest access to key talent from partners. Access to key talent under an acquisition will depend on the new leadership and how the new company is reorganized.

5.2.4 Market Share

As discussed in chapter 2, Company X has a portfolio of drug candidates targeting unmet medical needs in a large therapeutic market sector. To maximize value from its product portfolio, the company needs to get a reasonable market share. By so doing it will generate the required revenue to support its innovation. In licensing only and acquisition deals, the company would give up most of the potential product value including the market share to the licensee and the acquirer, respectively. On the other hand, a co-development alliance would allow the partners to split the market share.

5.2.5 Control of Company

To be able to execute its vision, goals and objectives Company X needs to have control. As mentioned in chapter 3, the company is led by a visionary Chairman who has founded and led two other companies, a CEO with extensive business management experience, and a solid Board of Directors. An acquisition would leave the company with the least control of its future direction, while a co-development alliance would require the company to cede substantial control

to the partner. A licensing agreement would give the company the greatest control of its internal activities.

5.2.6 Portfolio Synergy

As mentioned in chapter 3, Company X has a portfolio of products that are appropriate for a partnership strategy because they are novel, proprietary and target large markets of unmet medical need. Portfolio synergy in an alliance deal is important for the overall strategies and objectives of the firm. Potential partners have different demands and capabilities, and for a firm to attract them, there has to be some portfolio synergy. In licensing and co-development alliance deals, a high portfolio synergy is required. Given that acquisitions are often done for strategic reasons they would have a medium portfolio synergy overall.

5.3 Summary of Evaluation of Strategic Alternatives

The evaluation criteria were based on goals of the company, weighted by importance in regards to the strategic alternatives available to Company X (Table 4). Short term cash flow was assigned the highest weighting because Company X only has enough money to last till the fourth quarter of 2007. The company's core competence is innovation, and it needs cash to support the high costs of R&D. To sustain its core competence in innovation, Company X needs a more reliable source of financing, particularly given its location in Vancouver where there is short supply of local venture capital. Long term profitability would provide reliable financing to support R&D, hence it was assigned the second highest weighting. After securing reliable access to capital, Company X needs the appropriate talent to conceive, develop and manage its innovation. Again, this is important in Vancouver where there is short supply of top scientific and managerial talent in the CNS sector. Having secured adequate cash and talent to support and develop its innovation, the next important criteria would be market share to maximize product value including royalties from sales. This would provide additional revenue to be infused into

innovation. At the same time, to be able to focus on its core competence in innovation and execute its vision, goals and objectives, the Company X needs to have control. Finally, Company X has a portfolio of drug candidates targeting major unmet medical needs in a large market sector, and it will need portfolio synergy with potential partners to have a successful alliance. The strength of each strategic alternative in relation to the criteria was ranked from low to high. Based on this evaluation, a licensing & co-development alternative would have the strongest position in relation to the strategic goals of Company X, or better the selected criteria and their weighting.

Table 4 Evaluation of Strategic Alternatives

Goals	Weight	Strategic Alternatives			
		S1	S2	S3	S4
Short term cash flow	2.5	Medium	Med/Low	Low	High
Long term profitability	2	Medium	High	High	Low
Access to top talent	1.5	Low	High	High	Medium
Market share	1.5	Low	Med/Low	Med	Low
Control of company	1.5	High	High	Med	Low
Portfolio synergy	1	High	High	High	Medium
Total Adjusted Score	10	19.5	24	22	17.5

S1 = Licensing Only; S2 = Licensing and Co-development; S3 = Co-development Only; S4 = Acquisition. Evaluation: High = 3; Medium (Med) = 2; Med/Low = 1.5; Low = 1.

The next chapter uses this analysis of alternatives weighted against criteria of importance to Company X and makes some recommendations.

6 RECOMMENDATIONS AND CONCLUSION

This project recommends that Company X should adopt a strategy of licensing and co-development in parallel. This strategic alternative is detailed in section 5.1.2. Company X should focus on its core competence in innovative research on novel compounds for the treatment of CNS disorders, and develop the drug candidates up to the end of Phase I clinical trials. The company should then out-license one half of the compounds that successfully complete Phase I clinical trials, while retaining the other half for a co-development alliance. A licensing deal would infuse a significant amount of cash into the company to support its R&D activities, and to generate additional compounds for future deals or commercial considerations. For the out-licensed compounds, the firm will also avoid the high costs and risks of drug development and regulatory approval, in which it has no expertise.

By forming a co-development alliance for the other half of its Phase I compounds, the company stands to benefit from the financial resources, regulatory, manufacturing, sales and promotion expertise from the big pharmaceutical partner. Moreover, the risks of drug development and regulatory approval, as well as the profits from product sales would be shared, thus creating higher incentives for successful partnerships. Overall, a parallel licensing and co-development strategy would offer significant short term cash flow for R&D, and also provide financial resources, regulatory and commercialization expertise to enable the company get its products on the market. Furthermore, a co-development alliance with a large partner would boost investor confidence in the firm.

The global CNS drug industry presents an attractive therapeutic sector to new firms because of its rapid growth, unmet medical needs, low rivalry and absence of significant barriers

to entry. The rapid growth of the CNS industry is expected to continue over the next ten years with the increasing proportion of the ageing population in western societies. Many of the CNS disorders have unmet medical needs, and current treatment methods are mainly symptomatic. Therefore, there is a wide range of opportunities for increased R&D to generate better drugs for these ailments. As a result of this attractiveness, Company X should continue investing in this industry and focus on its competence in innovative CNS research to develop more compounds.

On the whole, rivalry in the CNS industry is low, mainly because the participating pharmaceutical and biotechnology firms have differentiated strategies, patents and semi-exclusivity based on the wide range of disorders in this therapeutic category. The only significant barrier to entry for new companies is capital requirements, thus the threat of entry is medium. The threat of substitute products is also medium, because if a firm develops safer and more effective drugs, patents may protect it from alternative products for a period of time. The overall power of suppliers is medium. This is because the suppliers of human and financial capital are in short supply, whereas the number of firms who provide raw materials is large and they can enter the market easily. On the whole, the power of buyers is medium, given that the high bargaining power of hospitals is balanced with the low bargaining power of doctors, pharmacies and patients.

To be successful in the CNS industry Company X needs improved R&D efficiency, access to capital, alliances, human resources and location in a major cluster. Innovative technologies and products are vital for success. Financing is crucial for the costly R&D, clinical development and approval phases. Through strategic alliances, the company may gain access to expertise, resources, funding and new products. Skilled managerial and scientific talent is scarce in the CNS industry sector, and the firm will need to attract, reward and retain them.

The company should focus on further building its core competence in CNS research. Its Scientific Advisory Board with leading scientific experts in CNS disorders reflects this strength.

In addition, the company has a visionary Chairman, an experienced CEO and a reputable Board of Directors. On the other hand, Company X needs to address its areas of weakness. Despite its great science and innovative compounds, the company has no products on the market and no sales revenues. In addition, it has no manufacturing and commercialization capabilities so it will have to rely on other companies' expertise. Being a small company, it may not be able to provide financial rewards that larger firms offer to attract and retain top-tier employees.

The company should take advantage of the wide range of opportunities in the CNS drug industry. Its innovative and proprietary products target large markets with unmet medical needs. The company has intellectual property patent protection for these compounds. The global CNS drug industry was estimated at \$87 billion in 2004, with an annual growth rate of 9% (IMS World Review, 2005). This growth rate is expected to increase rapidly over the next ten years, thus presenting a good business opportunity to the company. The current strategy of the company is to develop the compounds up to the end of Phase I clinical trial and then seek licensing, acquisition, co-development and partnering deals with value-added biotechnology and pharmaceutical companies.

To be able to attract good deals Company X should continue focusing on the CNS disorders with large future market size given the increasing percentage of the ageing population. The company should concentrate on using its technology platform to develop novel first-in-class compounds and new treatment options that would secure large payments from potential partners. A product pipeline with many compounds, reflecting a risk balanced drug portfolio would be more appealing to potential alliance partners.

To secure good deals Company X needs to have supportive positive clinical trial data. Focusing on chronic indications such as Alzheimer's disease is a good strategy, because such disorders are associated with larger deals in comparison to acute indications. Given that deals on

biologics tend to be valued more compared to NCE deals, the company should continue developing its novel peptide compounds which are biologics.

To be able to command large size deals, Company X will need to have third party endorsement of its compounds. Validation by an independent body or institution will give the potential licensee more confidence in the compounds. In addition, the company should focus on drug candidates that exhibit significant advantages over current therapies. Such products will not only secure good deals, but they will also have a better chance of getting regulatory approval. The company should strive to advance its products to late-stage in order to retain more potential value of the products.

Taking into account the CNS industry analysis, the internal analysis, the strategic alliance deal analysis and the evaluation of the strategic alternatives, this study recommends that that Company X should adopt a strategy of licensing and co-development in parallel. The global CNS drug industry is attractive because of its rapid growth, unmet medical needs, low rivalry and absence of significant barriers to entry. Therefore, there is a wide range of opportunities available to Company X in this market. To be successful in the CNS industry, Company X needs improved R&D efficiency, access to capital, alliances, human resources and location in a major cluster. To attract good deals from potential alliance partners, Company X needs to advance its compounds in clinical trials, obtain good clinical trial data and target large market opportunities. It also needs to develop proprietary technology platforms capable of delivering a stream of products, including first-in-class drug candidates. Furthermore, the company needs to develop drug candidates with significant advantages over current treatment methods, obtain third party endorsement and preferably target chronic indications to maximize potential product value.

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