THE EMERGING NANOMARKET WITH NEW BUSINESS ENVIRONMENT

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ABSTRACT

An examination of the key factors in choosing alliances between biotechnology start-ups and pharmaceutical firms. The Recap Alliances database is utilized to determine the successful combinations of factors for alliance-forming decision making. An ordinary least-squares (OLS) model is implemented to determine the most critical success factors and a constrained regression model is implemented in determining which resulting factors of interest are complements and which are substitutes in terms of profit of the alliance venture. The results shed light on what factors biotechnology startups and pharmaceutical firms should be looking for in potential partners in order to give themselves the greatest chance of success in terms of profit and profit growth, respectively.Keywords: Biotechnology, Complementarity,Constrained,Regression

INTRODUCTION

Pharmaceutical firms, like most firms in any industry, are continuously searching for the most efficient methods for generating profits. There are many strategies they use, amongst which is to partner with start-up companies in order to develop new products. These alliances can result in developing more products for the market faster, but do the costs outweigh the benefits? One way to analyze these relationships and their resulting effects on the profitability of the alliances is to empirically search historical data on these relationships and determine which variables have the most effect on success. This is most common and can be analyzed using common regression analysis techniques. In this paper, we take an additional unique approach in that we also look into whether the variables that are the most discerning factors of success are complementary to each other or substitutes for each other. This is known as complementary analysis and can be performed using constrained regression. This kind of analysis gives additional insight into the intricacies of the alliances between big pharmaceutical firms and their alliances with start-up firms.

LITERATURE REVIEW

Characteristics and causes of growth in biotech firms

The rapid growth of biotechnology firms is not completely due to alliances. In fact alliances sometimes prove to be unsuccessful (Niosi, 2002). For example, alliances between large pharmaceutical companies and small biotech firms may have a "negative effect on their subsequent partnering (Roijakkers, Hagedoorn, and Kranenburg, 2005). This is due to the low mutual dependency levels, low similarity and low equality levels between them. However, as much as alliances play important part, other factors also contribute to biotech firms' growth.

In order for biotech firms to be successful they need to have strong local relations in order to attract investment (Gertler and Levitte, 2005). This also helps small biotech firms to have strategic as well as research and development partnerships, which are more important for them at their stage than they are important for large biotech firms (Audretsch and Feldman, 2003). Furthermore, having in-licensing agreements with universities help biotech firms have a better chance of attracting "revenue-generating alliances" with downstream partnerships. The academic relationship between the firm and the university also influences the chances for a biotech firm to obtain commercialization rights on scientific discoveries made at the involved universities (Stuart, Ozdemir, and Ding, 2007). Hence, it is important for such firms to have strong academic relationships through in-licensing agreements, as they play a role in their success and financial attractiveness.

In their study of start-up funding sources and biotechnology firm growth, Ahmed and Cozzarin (2009) highlighted the concerns about start-up financing and their impact on firm's growth and performance. With reference to the results of their two extensive surveys of the Canadian biotechnology sector in 1991 and 2001, they demonstrated that angel, venture and conventional capital have contributed significantly to Research and Development

(R&D) capital formation and sales growth. Also, the contribution of funding from government, Initial Public Offering (IPO) and alliance capital sources are unimportant for the sample of biotechnology firms in Canada (Ahmed and Cozzarin, 2009).

There are certain features and phases that need to be gone through by biotech firms in order to speed up the growth process. These milestones include gaining patents and obtaining venture capital. Also, having strong research and development as well as entry into the stock market, having significantly large alliances, and exporting products internationally are part of these milestones (Niosi, 2002). Each one of them is an important contributor to the success and growth of biotech firms.

Research and development in biotech firms

There are two major ways of conducting research and development; through, in-house research and through contract/collaboration research. In-house research is important for having innovation in biotech firms which is n important factor for their success (Gertler and Levitte, 2005). Thus, technological advancements are necessary to be available in-house for high levels of innovation to take place. An example of companies which rely on in-house research more than external dependence on organizations, are Japanese bio-tech firms (Kneller, 2003). This allows them to be innovative and to discover their own drugs. However, in-house research has many obstacles that make it difficult to pursue. These obstacles include the continuous advancement of new bioinformatics knowledge which is beyond the capacity of any large biotech firm to be up-to-date with. Also, other obstacles include, having in-house research teams of MS graduates that have limited innovative capabilities, as well as having workers that are not completely committed and loyal to their research.

As much as there are benefits for having in-house research capabilities, not all biotech firms have the resources and capital to use it. When public market conditions are not doing well, biotech firms tend to resort to contract research with pharmaceutical firms to finance projects. Collaboration research is beneficial as it improves learning and speed of research as well as enhances flexibility and trust between collaborating firms (Lerner, Shane, and Tsai, 2002).

Equity links vs. alliances in biotech firms

Biotechnology firms tend to resort to equity links when it is more favorable to do so than to form alliances. These choices depend on the circumstances of the firm and its level of research engagement. When biotechnology firms have previous successful alliance experiences, it is less likely for them to have equity links and acquisitions (Carayannopoulos and Auster, 2010). However, if these firms are engaged in more risky research projects with unidentified outcomes, they are more inclined to have equity alliances. Also, if clients' investments of time and money are high or if the value of R&D is low it is more favorable for firms to have acquisitions and equity links. Moreover, if contracts are modified after they are signed or if they are at a stage of high risk in the R&D process, equity links are a better option (Filson and Morales, 2006). Also, if these firms have more acquisition experience or if the partner firms have moderate alliance experience, acquisitions are more likely to occur as much as sourcing knowledge is more useful through acquisitions if the

"knowledge domain is more complex and valuable" (Carayannopoulos and Auster, 2010).

The previously mentioned research proves that both equity links and alliances have their advantages and flaws. Although it can be inferred that equity links are more costly, they can be more advantageous when research projects involve high risk, value and investment as it provides more control to the acquirer over resources. In the case of alliances, control rights are determined according to the financial resources available for the firm. The allocation of control rights is not based on both firms' interest in "maximizing joint value", however, it is based on which one has the bigger financial capability. The higher the financial capabilities of the R&D firm (whether biotech or pharmaceutical), the more control it has over research and development decisions (Lerner and Merges, 1998).

In an attempt to understand how young biotechnology firms establish alliances with established organizations, Kim and Higgins (Kim and Higgins, 2007) examined the effect of upper echelons on attracting powerful intermediaries. Their research showed that alliance formation is related to status homophily and role-based homophily between young and established organizations.

Many researchers have attempted to explain why client firms in strategic alliances often purchase some of their R&D partner's equity. Filson and Morales (2006) determined that an equity link is less likely to be used when the R&D firm has more previous successful alliances. They also concluded that an equity link is more likely to be used when the project's outcome is more difficult to predict, the client's investment of effort and money is greater, the R&D firm's value is low, the contract is modified after the initial signing date, and the contract is signed during a stage of the project that involves a high risk of failure, high investment, or both.

Complementarity

In order to determine complementarities among a pair or group of organization qualities of an organization, a mathematical framework must be in place in order to test for specific, statistically significant evidence. Thus, a technical definition must be clearly defined as is done so in this section.

Two or more variables are called (Edgeworth) complementary if a higher value in any variable increases the marginal returns to higher values in the remaining variables. This simply means that increasing both values at once has a greater return than increasing the variables one at a time. In more precise terms two elements are complementary in the objective function if they satisfy the supermodularity restrictions.

Further, given a real-valued function f on a lattice X, f is supermodular and its arguments are (Edgeworth) complements if and only if for any x, y in X, $f(x) - f(x \cap y) \geq f(x \cup y) - f(y)$. In this case, $x \cap y$ is the greatest lower bound between x and y and $x \cup y$ is the least upper bound between x and y. If f is twice continuously differentiable, the defining condition is equivalent to nonnegative mixed-partial derivatives (Milgrom and Roberts, 1995).

There are several independent definitions of complementarity in various other fields of research, such as physics for example. Depending on which definition is used to

describe complementarity, a different technique is used. For this paper, complementarity refers to the Edgeworth definition described here.

In order to determine complementarity, there are several methods available. Using a least-squares method (Shepard, McDermott and Stock, 2000) is the most straightforward approach in which there are several variables to consider. These models are used to determine which variables are positively or negatively correlated and therefore which elements show evidence of complementarity to one another. For the most part this is a reasonable approach, but has several drawbacks. One of the biggest concerns with using a least-squares method according to Athey and Stern (1998) is that a positive correlation in the unobservable results in a positive bias in the estimate of the interaction effects. This is further stated by Lokshin, Carree, and Belderbos (2004). In addition, if the practices are complementary in the design phases, then the interaction effect will be understated. Thus, the regression techniques may find complementarity when none exists or not find it when it is present. This technique was used to confirm results from this study but are omitted from the paper.

Another more recently introduced method is the parametric method. This technique involves showing that the function that's being investigated is supermodular in each pair of elements. This model doesn't have the biases and limitations of the least-squares technique. The method relies on a technique called "switching regression" which is used by Athey and Stern (1998) and places a restriction on the variation of the interactions between variables. This ultimately allows researchers to draw unambiguous policy conclusions about the interaction effects between variables. This method was recently used by Mohnen and Roller (2005) to determine complementarities between problems related to innovation and the probability of having an innovation. The results obtained from this method are heavily dependent on accurate estimations of the coefficients in its objective function. Also, it has been shown to be unreliable for several variables being investigated simultaneously for complementarity. For this reason, only pair-wise comparisons are focused upon in this paper in the complementarity analysis.

Recent work by Lokshin *et al* (2004) propose a testing procedure for complementarity and substitutability that can be used for multiple practices. The method can handle the case of continuously measured practices as well as dichotomous practices. The approach uses a structural estimation framework, applies inequality constrained least-squares estimation, and results in an alternative testing procedure comparable to recently used methods as described previously (e.g. (Athey and Stern, 1998; Bresnahan, Brynjolfsson, and Hit, 2002). This technique has the potential to be useful for future research in the field when continuous variables are analyzed.

DATA SET

The Recap Alliances database (see www.recap.com for more information) currently contains 23,786 fully-searchable high-level summaries of biotech alliances commenced since 1973. Recap analysts mine several industry news sources each day, recording each biomedical alliance, together with the source document. A multitude of specific characteristics for each alliance are tracked, such as: the alliance date and dates of revision, alliance type (e.g., license, sublicense, acquisition,

supply, etc.), product type/technology (e.g., synthetics, monoclonals, devices, etc.), stage of development, product disease categories, payment amounts and types (upfront, equity, R&D, milestone, and royalty amounts, where available), the types of parties involved (e.g., Biotech, Pharma, University).

During preliminary OLS analysis, the variables representing R&D expenditure of the pharmaceutical firm, whether it's an in-licensing or out-licensing deal, the size of the pharmaceutical firm, and the amount of support given from the pharmaceutical firm to the start-up were found to be most critical in the profit of alliances. These were examined further, using complementarity analysis for each of the product types in the database.

METHODOLOGY

Using the method developed by Athey and Stern (1998), a profit function was specified using the variables identified as significant in predicting profit, using OLS analysis. Overall, all data was adjusted to represent 2010 values.

The response variable (profit) function for a given product type *j* is defined as

$P_{ij} = \sum_{i=0}^{2^n-1} g_{ij} s_{ij} + e_j$, where n is the number of endogenous variables.

The variables s_{ij} define a set of state dummy variables representing state i for product type j. The dummy variables are defined using binary algebra convention (e.g., state seven of a four variant problem 0111, would be represented by s_{7j}). Using this function, the supermodularity constraints were then used as a set of restrictions on the coefficients of the variables.

Consider a small four variable problem. There exists 16 states ranging from 0000 (i.e., no variables are implemented), to 1111 (i.e., all four variables are implemented). The complementarity conditions for the first two elements to be complementary are written as $\gamma_{8+s} + \gamma_{4+s} \leq \gamma_{0+s} + \gamma_{12+s}$, where s = 0, 1, 2, 3.

The other 20 restrictions for the five pairs of remaining variables may be expressed in the same way. All 24 restrictions are required to be satisfied in order for the whole set to be considered complimentary. Since pair-wise complementarity between any subset of variables implies supermodularity over the subset, this implies the joint testing of four inequality constraints (Mohnen and Roller 2005). The profit function could be submodular, in which case the elements are substitutes. This property was tested by reversing the inequalities of the constraints.

Two types of hypothesis tests (supermodularity and submodularity) were conducted. Strict complements (substitutes) were detected by testing for supermodularity (submodularity) of the function as the null hypothesis. These tests determined which set of elements should be adopted simultaneously in order for a firm to obtain the optimal benefits and which set of elements should never be adopted simultaneously.

The hypothesis regarding supermodularity has strict equality as the null hypothesis and that the inequality is negative for the alternative. So in our example, for elements 1 and 2,

H0: $-\gamma_{0+s} + g_{4+s} + g_{8+s} - g_{12+s} = 0_{4+s}$, for all s = 0,1,2,3

H1: $-\gamma_{0+s} + g_{4+s} + g_{8+s} - g_{12+s} < 0$, for all s = 0,1,2,3

Notice that this test is a joint one-sided test whether two obstacles are strict complements. Under the hypothesis Sγ =0, where S is a 4x8 matrix in the example partitioned as $[S^0 \mid S^1 \mid S^2 \mid S^3]$, the joint restrictions are distributed as v = S $\hat{g}$~ N(0, S cov($\hat{g}$)S') , where cov($\hat{g}$) is the variance-covariance matrix of the estimated g coefficients. The base model was created without any of the complementarity restrictions. A constrained regression model, with the complementarity restrictions as constraints was then calculated for each pair-wise test. To obtain the significance using this test a likelihood ratio (LR) was calculated. The likelihood ratio test statistic is of the form LR = 2 [L(θ_U) - L(θ_U)], where θ_U is the unrestricted Maximum Likelihood estimate of θ, and θ_R is the restricted Maximum Likelihood estimate of θ. To implement the test we use the following: LR = n log (SSR_U)/ log (SSR_R), where SSR_U is the unrestricted sum of squared residuals and SSR_R is the restricted sum of squared residuals. Gourieroux, Holly, and Monfort (1982) show that the LR is similar to the Wald statistic method used by Mohnen and Roller (2005).

Similarly, the submodularity hypothesis had strict equality as the null hypothesis and that the inequality is positive as the alternative. So for elements 1 and 2,

H0: $-\gamma_{0+s} + g_{4+s} + g_{8+s} - g_{12+s} = 0$, for all s = 0,1,2,3

H1: $\gamma_{0+s} + g_{4+s} + g_{8+s} - g_{12+s} > 0$, for all s = 0,1,2,3

This test accepts H1 when the constraints are jointly positive, and the elements are therefore strict substitutes. To obtain the significance using this test, a likelihood ratio was once again calculated. As a result of this testing, there are three alternatives for the relationship between a pair of elements:

the elements are strict complements,

the elements are strict substitutes,

the elements have intermediate p-values for both tests and are neither strict complements, nor strict substitutes.

DATA ANALYSIS

Complementarity tests were performed to see which combinations of factors were complements and which were substitutes, for each of the product types given in the dataset. One example of a product type analyzed was synthetics. As mentioned previously, through OLS analysis, four variables were found to have the most affect in determining the profit of an alliance. They were broken down into binary variables in order to perform pairwise complementarity tests. The variables were defined as shown in table 1. Note that for variable data types, the industry average was given as the distinguishing line between the two binary values. Below the industry average was given as a binary value of zero, whereas the industry average of above was given a value of one.

Table 1 - Binary variable definitions and associated values used in complementarity analysis

VARIABLE description (variable name)	VARIABLE Values
Pharmaceutical firm's R&D expenditure on synthetics (R&D)	= 0 if expenditure is below the industry average; = 1 otherwise
An in-licensing or out-licensing deal (LICENSE)	= 0 for out-licensing deal; = 1 for in-licensing deal
Size (i.e. number of employees) of the large pharmaceutical firm (SIZE)	= 0 if size of the company is below the industry average; = 1 otherwise
Amount of support ($) given to the start-up firm (SUPPORT)	= 0 if the support is below the industry average; = 1 otherwise

The response (performance) variables analyzed for the dataset was profit and profit growth, respectively, on a per-employee basis (including employees from both the start-up and pharmaceutical firm.

Both complementarity (supermodularity) and substitution (submodularity) tests were performed for each pairwise combination of the 4 dependent variables. The results are shown in table 1 (complementarity) and table 2 (substitution), respectively

The complementarity results show that above average R&D is complementary with in-licensing deals and larger sized firms, respectively. In-house licensing is also complementary with larger firms. Finally, Larger firms are complementary with larger support given to the start-up firm.

For the substitution tests, R&D was shown to be a substitute with above average start-up firm support. This means a the pharmaceutical firm could should either invest above average to support their R&D or give above average support to the start-up firm, but not both, in order to increase profits.

Table 2 - Complementarity test results for synthetic products, with profit as the response variable.

	R&D	LICENSE	SIZE	SUPPORT
R&D	----	0.001*	0.000*	0.259
LICENSE	----	----	0.001*	0.120

SIZE	----	----	----	0.000*
SUPPORT	----	----	----	----

* indicates complementarity at the five percent significance level.

Table 3 - Substitution test results for synthetic products with performance as the response variable.

	R&D	LICENSE	SIZE	SUPPORT
R&D	----	0.568	0.674	0.031*
LICENSE	----	----	0.430	0.333
SIZE	----	----	----	0.788
SUPPORT	----	----	----	----

* indicates substitutes at the five percent significance level.

Similar analysis was conducted for other types of outputs (e.g. monoclonals, devices), but due to space limitations, are not discussed.

DISCUSSION AND CONCLUSION

As a result of determining empirically the most influential factors involved in profit in regards to alliances among start-ups and large pharmaceutical firms through OLS analysis and then complementarity analysis on those factors, a methodology was introduced for generating general strategies for determining what decisions to make in terms of R&D allocation within the large firm, monetary support from the large firm to the start-up firm, whether to create an in-license or out-license deal with the start-up firm, and finally the size of the large firm. These factors are among many factors that have been studied in the literature in regards to alliance performance. One specific example of the analysis methodology was demonstrated for the synthetics industry.

From the literature, it was shown that there are many factors that can play a significant role in determining the success of an alliance. These are generally very specific to the industry and environment. Thus, including more variables into the complementarity model could certainly provide more insight into the analysis given and thus, should be explored. However, the constrained regression constraints in the parametric complementarity model increase exponentially as the number of variables included in the model increases.

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