Product Complexity and Strategic Alliance on Drug Approval

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ABSTRACT

Management of the business-government relationship is critical for firm performance in regulated industries. In this paper, we predict a U-shaped relationship between product complexity and the time to approval by the US Food and Drug Administration (FDA). Moreover, we argue that this association is contingent on the types of strategic alliances (i.e., R&D alliance, Marketing alliance) of the focal firm in that those alliances help FDA and pharmaceutical companies achieve harmony. Using the approved drugs by FDA from 1999 to 2016 as the sample, our hypotheses are supported by the empirical analysis on US pharmaceutical firms. The findings have important implications to achieving harmony between pharmaceutical firms and regulatory agencies.

KEYWORDS

Product Complexity, Regulatory Approval, Harmony

INTRODUCTION

The recent Coronavirus (COVID-19) pandemic has brought light to some of the dilemmas in new drug development and approval. New drug introduction to the market poses a double-edged sword for governmental approval agencies such as the United States Food and Drug Administration (FDA). While governments certainly welcome the innovativeness and complexity of new drugs, they also desire to control the pace of approval to identify safety problems (Carpenter, 2014). Obviously, the government-business relationship is very important for firm performance and firm survival. And it is especially salient in regulated industries (Desai, 2016). Previous research on such relationships has been largely focused on the effect of public policy on firm performance (Hiatt & Sine, 2014), the responses that firms make to regulatory change (e.g., Kozhikode, 2016), and regulators' responses to firms' behaviors (Heese, Krishnan, & Moers, 2015; Hiatt & Park, 2013). However, little is known about regulatory agency responses to i) characteristics of firms' outcomes (e.g., how complexity of regulated products affects agency opinions), and ii) firms' efforts to lower the information asymmetries between government agencies and businesses (e.g., how firms signal quality of regulated products through the reputation of their partners with whom they collaborate). Given the importance of product complexity in the approval process of FDA, the lack of research on how product complexity in product regulatory approval is certainly surprising. Our study fills this research gap by examining both the technical

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features of a product and market uncertainty that arises when firms launch these complex products.

Overall, government agencies are very powerful in regulated industries such as the pharmaceutical industry. The FDA, for example, "sustains a battery of powers" (Carpenter, 2014, p.1) in testing, marketing, labeling, advertising, and manufacturing of prescription drugs. In comparison, corporations have more limited powers in highly regulated industries. One question that arises is whether corporations can leverage their resources to gain power in the drug approval process to receive more favorable outcomes. Our answer is yes, and we base this conclusion on the premise that regulatory decisions are not based simply on power, but are determined by "a networked congeries of audiences" such as consumers, media organizations, science and business communities, and political forces (Carpenter, 2014, p10). Although there has been research examining the influence of regulatory agencies on firm outcomes (e.g., Kozhikode, 2016), theoretical extensions have been lacking. In this research, we argue that companies may leverage partnerships to expedite the approval process for complex drugs. The authorization of an emergency use for the antiviral drug, Remdesivir, is an example (FDA, 2020). In this paper, we argue that to promote social utility, government agencies, as governing bodies, take on the responsibilities to protect the interests of principals (i.e., citizens) to ensure an approved new drug "is almost certainly both safe and effective" (Carpenter, 2014, p.2). We argue that product complexity and strategic alliances may align the interests of the government agencies and the corporations, thus influencing the drug approval process.

By conducting this research, we make the following contributions. First, we examine the effect of product complexity on new drug approval, which impacts not only many people's lives but also the financial performance of producing companies (Galambos & Sturchio, 1998). By examining the specific contexts firms face when submitting drugs for regulatory approval, this study sheds light on how social forces and product complexity are intertwined in the regulatory process. Second, the findings of this study inform researchers about how the drug approval process is affected by product complexity. Our research is among the first studies to address how firms' partnerships alert stakeholders to the qualities of complex products, and how product complexity impacts marketing approval decisions by regulatory agencies. Third, from a methodological standpoint, we utilize a measure of product complexity not previously used in management research. Previous research on outcome complexity generally focuses on process complexity (Olausson & Berggren, 2010). Product complexity has been previously measured through consumer and manager perceptions (e.g., Swaminathan, 2003, Novak & Eppinger, 2001). However, no management scholar to our knowledge has objectively quantified product complexity. In the pharmaceutical industry, the chemical characteristics of new drugs are the primary information that FDA regulators consider in the approval process. Hence, we apply software used in chemical sciences to compute the molecular complexity of the drug molecule based on the bond connectivity and element diversity. In essence, this technical measure of product complexity provides a more objective way to capture the specific features of the drug product, and which has a strong linkage to regulatory agencies.

HYPOTHESES DEVELOPMENT

PRODUCT COMPLEXITY AND STRATEGIC ALLIANCES

Product complexity has been examined broadly across academic fields (e.g., Baldwin & Clark, 2000; Chan, 2000). The major findings are that product complexity not only increases the product enhancement effort (Banker et al., 1998) but also increases the interdependency among units within a firm (Baldwin & Clark, 2000; Winter & Szulanski, 2001). Specifically, high complexity demands frequent communication between different units within a firm to make innovative upgrades or modifications (Henderson & Clark, 1990). Furthermore, Henderson and Clark (1990) also argue that

the organization teams should establish high understanding and interdependencies to develop more complex products. Time to transfer complex technology or information is also required (Salomon & Martin, 2003). Because of these elevated costs, firms may ignore customers desires for increasingly complex products and focus on only incrementally innovative products (Ethiraj et al., 2012). In addition, even within a firm, decision-makers can be reluctant to pursue complex projects since they often require aggregation of dispersed information and heightened coordination (Henderson & Clark, 1990). In the setting of government-business relationships such as FDA approval, the influence of product complexity may entail additional complexity since it often involves collaboration among multiple firms and public institutions.

Strategic alliances formed during new drug development can provide information to the FDA about product quality that is otherwise unavailable, and, hence, collaboration often increases the likelihood of pharmaceutical regulatory approval (Carpenter, 2014). Firms not only obtain complementary resources from partners, but also achieve economies of scale/scope. The formation of alliances could help firms to exchange resources and assess their values (Diestre & Rajagopalan, 2012; Saxton, 1997). For instance, Li et al. (2008) find that partner selection acts as an important governance mechanism to protect the intellectual property in the alliance entity. Leiblein and Reuer (2004) find that strategic alliances can inhibit opportunistic behavior of the partners. These findings suggest that strategic alliances could improve company performance. Alliances, therefore, can signal high levels of potential product quality to regulatory agencies (Carpenter, 2014). Specifically, the characteristics of strategic alliances could have significant effects on firm outcomes (e.g., Gulati & Higgins, 2003), such as performance improvement (Sampson, 2007), knowledge acquirement (Novak & Eppinger, 2001), and lower market uncertainty (Baum, Calabrese, & Silverman, 2000; Diestre & Rajagopalan, 2012). In this paper, we argue that the effect of product complexity on time to approval is contingent on strategic alliances.

THE CURVILINEAR EFFECT OF PRODUCT COMPLEXITY ON TIME TO APPROVAL

Product complexity could signal heightened advancement potential for the technology embedded in the product. For drug companies, more complex drugs may experience quick approval from FDA, given that both parties (pharmaceutical companies and FDA) share the same object of pushing the effective drugs to the market as soon as possible. And some studies in medicinal chemistry have linked molecular complexity to efficacy of drugs (e.g., Caille et al., 2019). As drugs become more disease specific and safety requirements concomitantly increase, pharmaceutical development has necessitated more chemical complex compounds (Walters, Green, Weiss, & Murcko, 2011). Therefore, since speed to market of effective and safe treatments is one goal of the FDA, one would expect that increasing product complexity may shorten the time to approval from FDA. Greater complexity tends to suggest greater efficacy.

However, when product complexity is high, higher information asymmetry and concerns from FDA may be elevated as well. Higher complexity creates greater difficulty in a regulatory agency's understanding a drug's mechanisms, its adverse effects, and its unintended consequences. While the producing firm may have detailed knowledge of the drug due to its experience with it in research and development, regulatory agencies must rely on secondhand reports and filings for this knowledge (e.g., Holmstrom, 1989). This asymmetry, in turn, may prolong the time required for a drug to receive regulatory approval. Indeed, increases in chemical complexity often result in greater dissimilarity between the focal and previous drugs, reducing regulators' abilities to compare the focal drug with previously considered therapies (Walter et al., 2011). Novelty, in turn, leads to unforeseen obstacles, side-effects, and contingencies (e.g., Holmstrom, 1989), reducing likelihoods of approval.

Further, highly complex products tend to be associated with technical uncertainty that may result in ambiguity for regulatory agencies. Since highly complex products may have little structural similarity to previous products, regulatory agencies will have relative few previous "models" on which to base their decision (Holmstrom, 1989). These factors will tend to slow the process of regulatory approval.

Accordingly, we suggest that moderate levels of product complexity will lead to shortest approval times for new pharmaceuticals. Moderate complexity levels provide enough complexity to ensure novelty and chemical efficacy while mitigating against significant uncertainties that might cause delays in the FDA approval process. Consistently, when product complexity is relatively low, increasing product complexity may lead to shorter times to approval as efficacy rises with complexity. Rising complexity and attendant efficacy compel the FDA to speed regulatory approval. After a midpoint of complexity, however, increases in complexity reduce the FDA's ability to process and understand information in a timely manner. Increases in complexity at relatively high levels, therefore, increase approval times. Hence, we expect that there is curvilinear relationship between product complexity and time to approval from FDA.

Hypothesis 1: *There is a U-shaped relationship between product complexity and time to approval such that time to approval decreases from low to moderate product complexity and increases from moderate to high product complexity.*

THE MODERATING EFFECT OF STRATEGIC ALLIANCES

R&D ALLIANCES

For a complex product to receive regulatory approval, the producing company needs to provide enough information so that the regulatory agency could evaluate the product in an objective and complete manner. However, due to the difficulty a firm may have in transferring knowledge of complex products to the regulatory agency (Kogut & Zander, 1993; Szulanski, 1996), the regulatory agency will require considerable time to assess the feasibility and safety. We argue that strategic alliances can aid firms in transferring information to regulatory agencies.

An R&D alliance is one of the major vehicles that firms pursue to develop advanced technology for products or services, especially in the pharmaceutical industry (Hoang & Rothaermel, 2005; Oxley & Sampson, 2004; Sampson, 2007). R&D alliances could improve firms' innovation performance significantly compared with firms without R&D alliances (Sampson, 2007).

In the context of pharmaceutical industry, the involvement of an R&D partner when developing a complex product indicates that the focal firm has invested a significant amount of time and energy to produce the advanced technology (Hoang & Rothaermel, 2005). As noted, collaboration often increases the likelihood of pharmaceutical regulatory approval (Carpenter, 2014). Firms obtain complementary resources from partners and achieve economies of scale/scope. Strategic alliances can inhibit the opportunistic behavior of the partners (Leiblein & Reurer, 2004), further improving alliance performance. Hence, alliance can signal the reliability and feasibility of the technology thereby, reducing the agency's concerns on safety and adverse selection problem.

In sum, R&D alliances harmonize the joint effort by corporations and government agencies. R&D agreements may reduce the cost associated with the drug development process (Shan, Walker, & Kogut, 1994) and provide firms more access to financial resources (Gerlach, 1992). Further, R&D alliances give government agencies assurance that technical uncertainty may be mitigated due to the joint effort by several companies. Therefore, we predict that the time to get approved by regulatory agency will be shortened as the focal firm has more partners in R&D alliances for a certain level of product complexity.

Hypothesis 2: *The number of the focal firm's partners in R&D alliance moderates the U-shaped relationship between product complexity and time to approval in such a way that as the number of R&D alliance partners increases, time to approval is reduced.*

MARKETING ALLIANCES

Marketing alliances are an important vehicle used to build customer awareness and complement the products from each partner (Anderson & Narus, 1990; Bucklin & Sengupta, 1993). Marketing alliances involve the partners' collaboration in the marketplace for increasing market share of each other's products (Bucklin & Sengupta, 1993). These alliances allow partners to contribute their unique resources and strengths to the partnership, in order to lower the market uncertainty associated with the new product. Each company shares knowledge it has developed so that the likelihood of success in launching the new product is higher (Baum, Calabrese, & Silverman, 2000; Diestre & Rajagopalan, 2012).

Marketing alliances could benefit the partner firms in at least two ways. First, partners can acquire from others new management and technological abilities (Dollinger, Golden, & Saxton, 1997), and access scarce resource (Wernerfelt, 1984). Second, forming a marketing alliance with reputable companies could lead to successful and innovative products since reputable partners provide a signal of quality for the focal firm (Granovetter, 1985; Hill, 1990; Saxton, 1997).

In the context of pharmaceutical industry, the launch of a new drug is associated with the safety and efficacy of the drug. Strategic marketing alliances are critically important for the introduction of the new product, especially when there is technologically advanced knowledge represented in the new product (Bucklin & Sengupta, 1993). Regulatory agency may also use this signal as an indication of the quality of the drug seeking regulatory approval. To some extent, marketing alliances could signal the future market potential of the product once the product is launched. Therefore, we predict that the number of marketing alliances in which a firm is involved also indicates harmony between government agencies and the firm. Marketing alliances act as a signal to the regulatory agency, thereby shortening approval times at all levels of complexity. In short, the number of marketing alliances should moderate the relationship between product complexity and time to approval.

Hypothesis 3: *The number of the focal firm's partners in marketing alliances moderates the U-shaped relationship between product complexity and time to approval in such a way that as the number of partners in marketing alliances increases, time to approval is reduced.*

METHODS

Data on New Molecular Entity and New Biologic drugs (NMEs) approved by US Food and Drug Administration from 1999 to 2016 was collected. NMEs cover a significant amount of customer market in U.S. Although there are significant differences in the structure of NME drugs and biologic drugs, the measurement used in this study is easily applied to both categories of drugs. Our sample consists of 482 FDA approved drugs in 18 years.

The Medtrack database was used to obtain the firm and chemistry data that is associated with each drug. Medtrack has been used in research about pharmaceutical industry (Diestre & Rajagopalan, 2012; Diestre, Rajagopalan, & Dutta, 2015) to provide firm-level information such as firm size, age, performance, R&D alliances, marketing alliances, corporate venture activities, and patent portfolios of firms across 17 therapeutic markets. Medtrack provides the marketed drugs and newly developed drugs for each firm as well as the active ingredient involved in each drug. The database also contains information regarding development stages of each drug, such as Research, Preclinical, Phase I, Phase

II, Phase III, Pending Approval, Approved, and Marketed. Each drug has a specific therapeutic domain based on its therapeutic properties and it contains a chemistry identifier.

PubChem database, an open source database, was used to collect the chemical structure information of each drug. The PubChem is a chemistry database which indexes all disclosed molecules in chemistry fields and assigns a Chemical Abstracts Service (CAS) number to each drug. By using CAS as the identifier, the chemical structure of each drug in our sample was specified and codified in PubChem database. Then a structural and elemental code of the drug molecule was used to compute the drug's complexity. Firm level data was collected from Compustat Industrial Annual database.

482 FDA approved drugs in 18 years consist of our sample. There are missing values about the development history in Medtrack database, which reduced our sample size. Moreover, other missing values about firm size and firm performance reduced our sample size to 344 observations.

DEPENDENT VARIABLE

Time to Approval was measured as the number of days between the start of Preclinical development and the date of approval by FDA.

INDEPENDENT VARIABLES

Product Complexity is measured by the molecular complexity of each drug. Each drug's molecular complexity is measured using PaDel-Descriptor. This open source software is a common tool in chemistry fields and has been used to compute molecule's various characteristics (Tripathi & Kumar, 2013; Yap, 2011). The molecular complexity in PaDeL-Descriptor measures a molecule's fragment complexity including functional groups, bonds, and the diversity of chemistry elements. PaDel-Descriptor uses the formula developed by Hendrickson et al. (1987) that has been considered as the primary measure of product complexity and can be applied to more different types of molecules than other methods. Complexity is calculated via the following functions:

$$C = C_\eta + C_E \quad (1)$$

$$C_\eta = 2\eta \, lg \, \eta - \Sigma_i \, \eta_i \, lg\eta_i \quad (2)$$

$$C_E = E \, lg \, E - \Sigma_j \, E_j \, lgE_j \quad (3)$$

The measure of molecular complexity (*C*) is a sum of two parts (equation 1): the first term C_η measures skeletal complexity as a function of bond connectivity (η); the second term, C_E, is a function of the diversity of elements, or atoms. Each of these terms also is composed of two parts: first (equation 2), an overall complexity term; and second (equation 3), a symmetry term subtracted from it to reduce the complexity to the extent that symmetry is present. This calculation integrates skeletal complexity as a function of bond connectivity and the diversity of elements. Therefore, our measure of molecular complexity is comprehensive and counts both structural diversity and the elemental diversity. PaDel-Descriptor uses the approach introduced by Hendrickson et al (1987) to compute the element complexity (Equation 3). Here, the work of Hendrickson et al (1987) is briefly introduced again to show the calculation of complexity, including the following equations and its derivatives. Although one can calculate molecular complexity based on three equations above, certain characteristics of atoms in molecule could be utilized to simplify the calculation such as Equation 2. In Equation 2, the computation of η for the whole molecule could use the following equation:

$$\eta = 1/2 \sum_i (4 - h_i)(3 - h_i) - D - 3T \qquad (4)$$

In Equation 4, h is the number of hydrogens on each non-hydrogen atoms. D is the number of double bonds. T is the number of triple bonds. Due to the different types of bond connectivity, the second item in Equation 2 is more complicated, given that central atom could have different patterns of symmetry term S_k. Therefore, the second item in Equation 2 becomes the add-up of symmetry term S_k of all equivalent atoms that follow the same pattern of symmetry. Then Equation 2 is derived to the following equation:

$$C_\eta = 2\eta \lg \eta - \sum_i (S_k)_i \qquad (5)$$
$$k = (3 - h)(2 - h) + \mathrm{R} \qquad (6)$$

k is the value of symmetry type; *h* is the number of hydrogen atom. Please refer to the work of Hendrickson et al (1987) for detailed information about the equations.

For the purpose of demonstration, here we choose two drugs (Replax and Reyataz) as the examples to show the molecular complexity. Figure 1 shows the chemistry structures of Replax and Reyataz. As can be seen, Replax (complexity=346.9) is less complex than Reyataz (complexity=841.44). Our data indicates that Replax took around 4 years to get approved by FDA, while Reyataz took around 9 years to get approved.

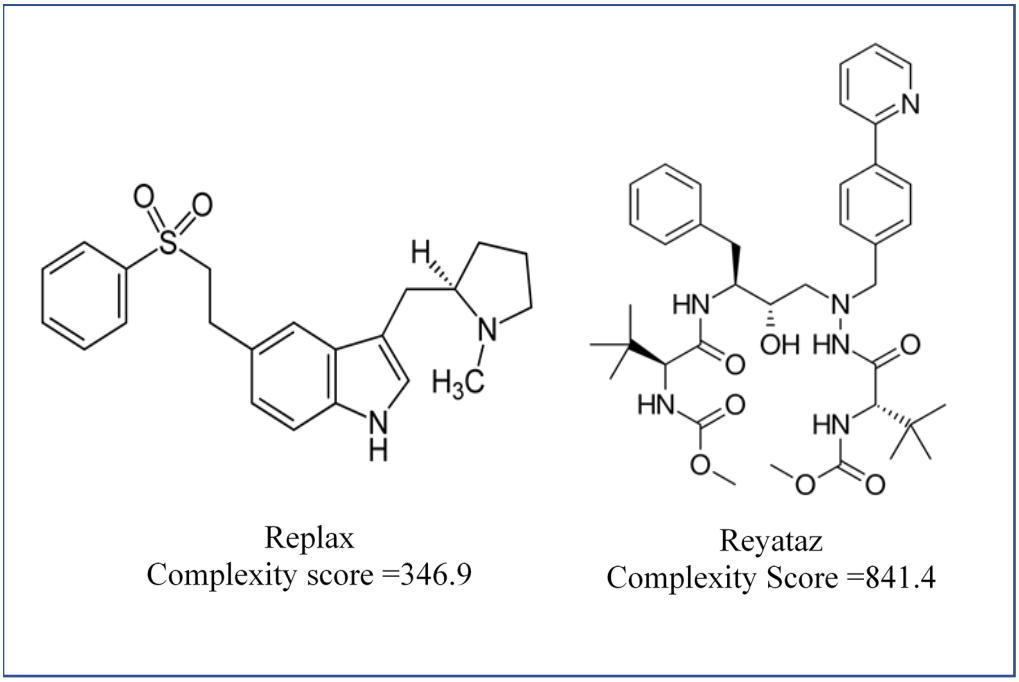

Figure 1. The Chemistry Structure of Replax and Reyataz

R&D Alliance is measured as the total number of partners in R&D alliance that the firm has for developing one focal drug.

Marketing Alliance is measured as the total number of partner companies that the focal company has for marketing the new drug.

CONTROL VARIABLES

To mitigate confounding effect, various firm level variables were included in the analysis. Firm size was measured as the number of employees (Miller & Cardinal, 1994; Zhang et al., 2007), and was obtained from the Compustat database. Firm size is logarithmically transformed in the model. Past firm performance is measured as return on assets (ROA) in the previous year (Wowak et al., 2011). In pharmaceutical firms, research and development expense is very important for developing new drugs. High R&D expense could signal the technical reliability of the new drug. Therefore, R&D expense on drug developments was also controlled. Firm leverage to control for the firm's tendency to use debt capital was also included as a control variable. This variable was measured as the ratio of total debt to total assets in order to control for the effect of firms' differences in capital on the choice of drug development (Geringer et al., 2000; Tallman & Li, 1996). To partial out the effects of macroenvironment, year fixed effect was also included in the analysis.

EMPIRICAL METHOD

The dependent variable is the number of days from the application of drug to the drug gets approved by FDA, which is a count variable and only takes non-negative integer values. Ordinary Least Square (OLS) regression assumes homoskedastic and normal distribution of error terms. The counted nature of our dependent variable violates those two assumptions. Therefore, negative binomial regression (which accounts for a Poisson distribution of our dependent variable) was used to estimate our empirical models (e.g., George, Wiklund, & Zahra, 2005; Sanders, 2001). In order to address potential multicollinearity problems, all the independent variables (except the year dummy variables) are standardized before entering the empirical analysis. All the values of the variance inflation factor (VIF) are lower than 4.95 in all the models, below the threshold value of 10 (Neter et al., 1985). So, multicollinearity is not a concern in our analysis.

RESULTS

Descriptive statistics, including means, standard deviations, and correlations are provided in Table 1. The average time to get approved by FDA is 1,014 days (3 years), which is consistent with the previous findings (Choi & Contractor, 2016; Munos, 2009; Scillittoe et al., 2015). Firm leverage is negatively correlated with the time to get approved (-0.11, $p < 0.05$). R&D alliance is also negatively correlated with time to approval (-0.12, $p < 0.05$).

Table 1. Descriptive Statistics and Correlation Matrix

Variable	Mean	Std Dev	1	2	3	4	5	6	7
1. Time to Approval (hundred)	*10.14*	*10.25*							
2. Firm Size[a]	*3.45*	*1.82*	*0.10+*						
3. R&D Expense (million)	*3.92*	*2.86*	*-0.06*	*0.68****					
4. Firm Leverage	*0.12*	*0.11*	*-0.11**	*-0.20****	*-0.10+*				
5. Firm Performance	*0.08*	*0.11*	*0.08*	*0.54****	*0.16***	*-0.24**			
6. Product Complexity (thousand)	*0.34*	*1.12*	*0.08*	*-0.01*	*-0.08*	*-0.13*	*0.05*		
7. R&D Alliance	*2.24*	*1.72*	*-0.12**	*-0.25****	*0.05*	*0.05*	*-0.26****	*-0.04*	
8. Marketing Alliance	*4.16*	*5.16*	*-0.07*	*-0.01*	*0.03*	*0.02*	*0.09*	*0.14**	*0.31****

N=344
[a] Logarithmically transformed
+ p < .10, * p < .05, ** p < .01, *** p < .001

Table 2 presents the regression results of testing our hypotheses. Model 1 includes control variables, Model 2 includes controls and the main effect of product complexity, and Model 3 includes controls, main effects, and the moderating effects of R&D alliance. Model 6 includes controls, main effects, and the moderating effects of Marketing Alliance. The results of Model 1 show that R&D expense (-0.593, $p < 0.01$) and firm leverage (-0.234, $p < 0.01$) significantly decrease the time to approval. However, firm size increases the time to approval (0.781, $p < 0.001$), indicating that bigger firms tend to take longer time to get approved by FDA.

Table 2. The Effect of Product Complexity on Time to Approval

Variables	Model 1		Model 2		Model 3	
Firm Size	*0.781***	*(0.196)*	*0.784***	*(0.194)*	*0.789***	*(0.195)*
R&D Expense	*-0.593***	*(0.194)*	*-0.635***	*(0.193)*	*-0.692***	*(0.190)*
Firm Leverage	*-0.234***	*(0.090)*	*-0.260***	*(0.089)*	*-0.267***	*(0.091)*
Firm Performance	*-0.176**	*(0.079)*	*-0.126*	*(0.078)*	*-0.116*	*(0.077)*
R&D Alliance	*0.082*	*(0.071)*	*0.108*	*(0.073)*	*0.292**	*(0.133)*
Marketing Alliance						
Product Complexity	*0.277***	*(0.097)*	*-0.409*	*(0.296)*	*-0.195*	*(0.303)*
Product Complexity_Squared			*0.092**	*(0.042)*	*0.020*	*(0.040)*
Product Complexity X R&D Alliance					*0.964+*	*(0.521)*
Product Complexity_Squared X R&D Alliance					*-0.212***	*(0.069)*
Product Complexity X Marketing Alliance						
Product Complexity_Squared X Marketing Alliance						
Constant	*8.756****	*(0.382)*	*8.5588****	*(0.393)*	*8.552****	*(0.386)*
Oberservations	*344*		*344*		*344*	
Log Pseudolikelihood	*-2889.9*		*-2887.9*		*-2882.1*	
Wald Chi-squared	*262.4****		*311.2****		*316.4****	
	Model 4		**Model 5**		**Model 6**	
Firm Size	*0.763****	*(0.199)*	*0.766****	*(0.198)*	*0.813****	*(0.197)*
R&D Expense	*-0.576***	*(0.196)*	*-0.616***	*(0.195)*	*-0.715****	*(0.196)*
Firm Leverage	*-0.239***	*(0.089)*	*-0.267***	*(0.090)*	*-0.287***	*(0.087)*
Firm Performance	*-0.201***	*(0.076)*	*-0.162**	*(0.075)*	*-0.136+*	*(0.072)*
R&D Alliance						
Marketing Alliance	*0.049*	*(0.064)*	*0.076*	*(0.065)*	*0.173**	*(0.068)*
Product Complexity	*0.266***	*(0.097)*	*-0.426*	*(0.301)*	*-0.823**	*(0.420)*
Product Complexity_Squared			*0.092**	*(0.042)*	*0.148***	*(0.053)*
Product Complexity X R&D Alliance						
Product Complexity_Squared X R&D Alliance						
Product Complexity X Marketing Alliance					*0.533**	*(0.225)*
Product Complexity_Squared X Marketing Alliance					*-0.088***	*(0.029)*
Constant	*8.751****	*(0.383)*	*8.553****	*(0.395)*	*8.364****	*(0.416)*
Oberservations	*344*		*344*		*344*	
Log Pseudolikelihood	*-2890.1*		*-2888.2*		*-2883.4*	
Wald Chi-squared	*245.6****		*280.1****		*294.6****	

N=344. Robust standard errors in parentheses. Year dummies are not reported here for brevity.
+ p<0.10, * p<0.05, ** p<0.01, *** p<0.001. Two-tailed tests.

Hypothesis 1 predicted that a curved relationship between product complexity and the time to get approved. The results of Model 2 and Model 5 in Table 2 show that the beta coefficient of the squared term of product complexity is significantly related to the approval time ($\beta = 0.092$, $p < 0.05$; $\beta = 0.092$, $p < 0.05$). Therefore, Hypothesis 1 is supported. Model 5 confirms this supporting. Figure 2 depicts the relationship between product complexity and time to approval. The values of product complexity are taken as the percentiles in the sample. As product complexity increases, time to approval is shortened. However, higher product complexity leads to longer time to approval as product complexity is high, which confirms the curve-shaped relationship.

Hypothesis 2 proposed that the relationship between product complexity and approval time will be moderated as the number of a firm's partners in R&D alliance increases in such a way that time to approval is shortened for either low complex or high complex products. The results of Model 3 in Table 2 indicate that R&D alliance has a negative moderating effect on the relationship between time to approval and the squared term of product complexity ($\beta = -0.212$, $p < 0.01$). Figure 3 is generated to present this negative moderating effect. The values of R&D alliance are taken as one standard deviation below and above the mean value. The values of product complexity are taken as the percentiles in the sample. As shown, as the number of partners in R&D alliance increases, approval time is shortened for either low product complexity or high product complexity. Therefore, Hypothesis 2 is supported. The post estimation analysis indicates that time to approval decreases 317 days when increasing forming one more partner in R&D alliance at the average level of product complexity.

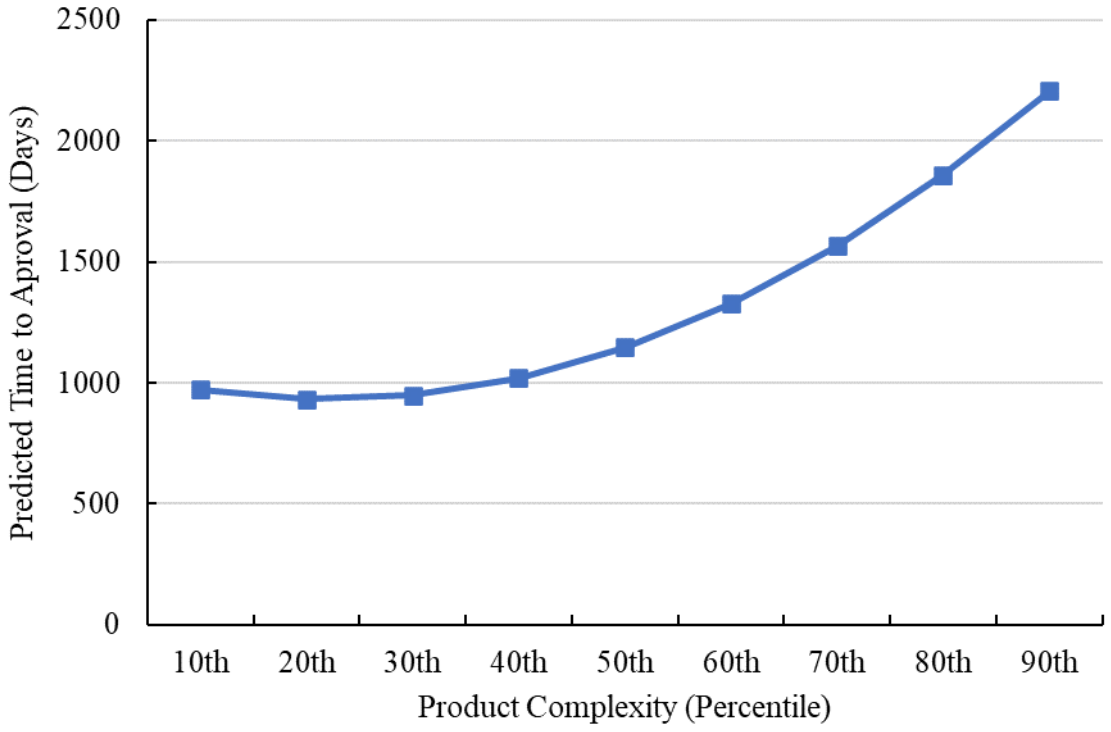

Figure 2. The Effect of Product Complexity on Time to Approval

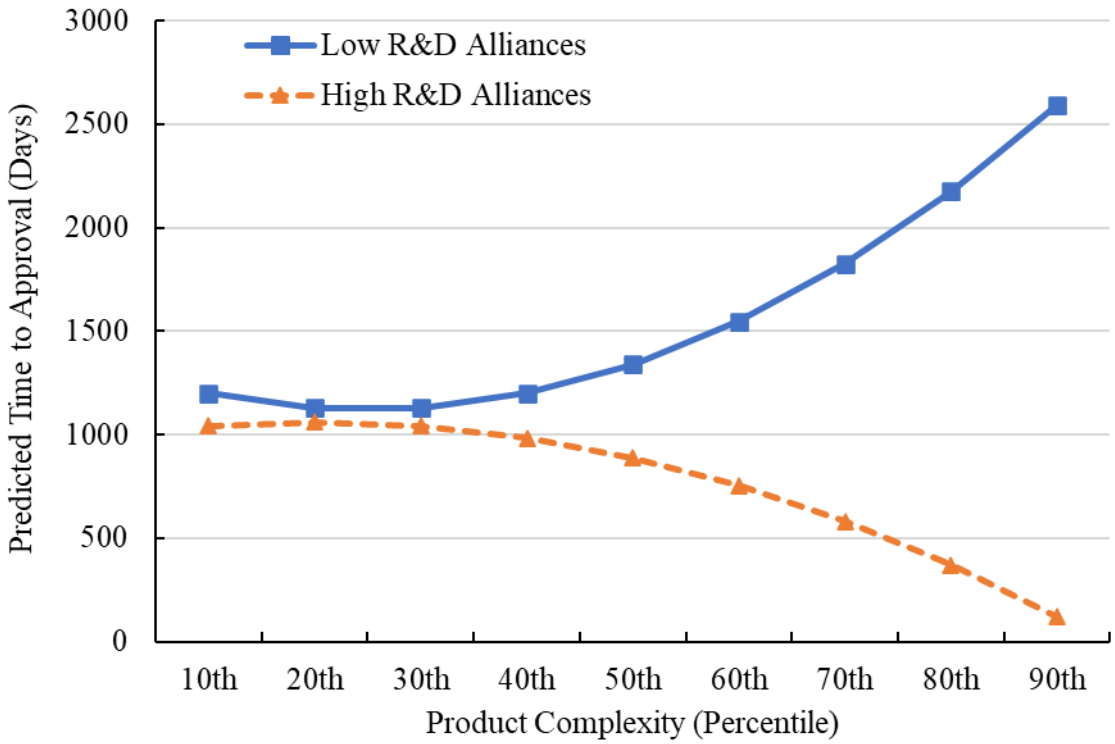

Figure 3. The Moderating Effect of R&D Alliance on the Relationship between Product Complexity and Time to Approval

Hypothesis 3 states that a firm's marketing alliances moderate the U-shaped relationship between product complexity and time to approval in such a way that as the number of the focal firm's partners in marketing alliances increases, time to approval is shortened for either low complex or high complex products. The results of Model 6 in Table 2 show that marketing alliances significantly moderate the effect of product complexity squared (β = -0.088, $p < 0.01$). Figure 4 also shows the significant moderating effect of marketing alliances. It shows that as the number of partners in marketing alliances increases, the approval time is shortened. Therefore, Hypothesis 3 is supported. The post estimation analysis indicates that time to approval decreases 90 days when there is one more partner in marketing alliance at the average level of product complexity.

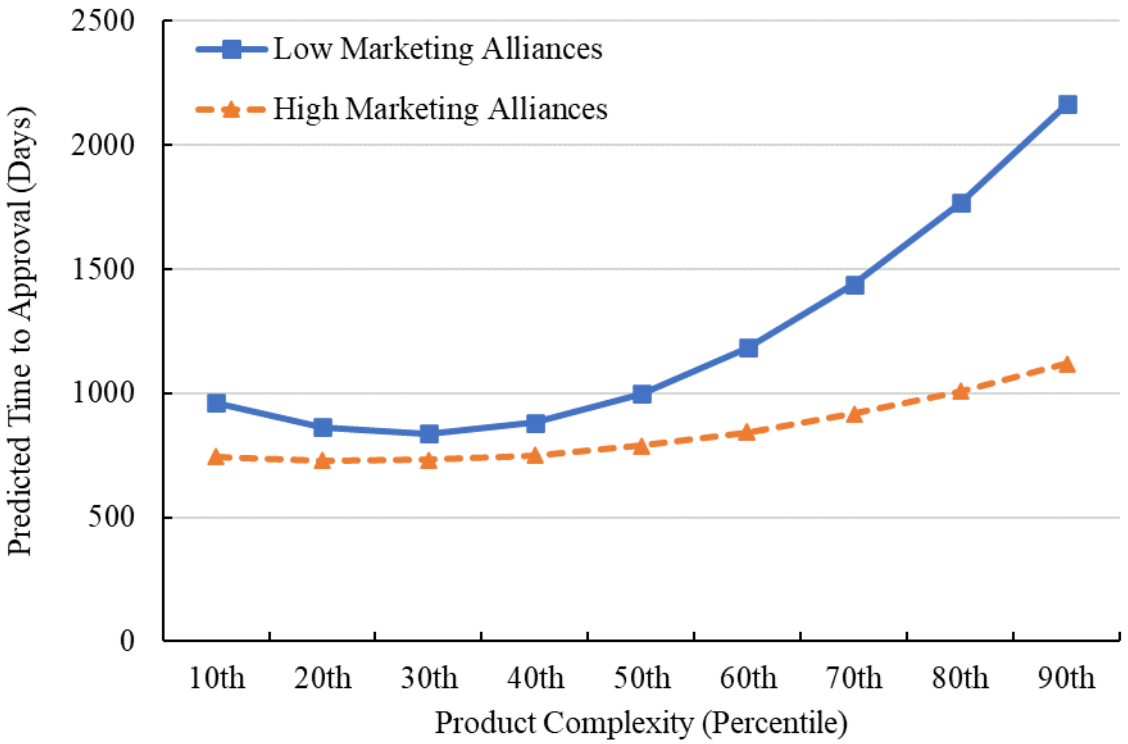

Figure 4. The Moderating Effect of Marketing Alliance on the Relationship between Product Complexity and Time to Approval

Since our interest in this research is about the relationship between product complexity and time to approval, only approved drugs are included in the sample. On one hand, this sampling to some extent matches our research questions and theoretical development. However, it may potentially introduce selection bias problem. Therefore, to address this problem, a Heckman Selection analysis was conducted by using the sample of 344 approved drugs and 160 failed drugs. A Probit regression was performed in the first stage. In the first stage, a binary variable created to indicate whether the drug was approved by the FDA or failed in clinical trials. This dichotomous variable was then regressed on firm size, R&D expense, molecular complexity, the number of indications, and the pharmaceutical class of the drug. An inverse Mills ratio generated from the first stage and controlling for the degree to which selection bias affects contaminates our estimations was added into the models in the second stage for predicting the time to approval. The results of the Heckman selection analysis are very consistent with the main results reported in the paper.

DISCUSSION

Our study extends the research about government-business relationships from the responses of the company to regulatory agencies. We argue that companies need to address technical uncertainty and market uncertainty associated with complex products in order to get products approved. The formation of strategic alliances, such as R&D alliance and marketing alliance could address this problem. By taking a sample of drug molecules from U.S. pharmaceutical companies, we find that there is a U-shaped relationship between product complexity and time to approval by FDA. This finding indicates that it takes shorter time for FDA to approve a new drug with increasing product complexity when product complexity is low. However, when product complexity is high, the FDA may require

more evidence to lower the technical uncertainty, increasing the time needed to reach the harmony between corporations and regulatory agency. As predicted, we find a negative moderating effect of R&D alliance and marketing alliance on the relationship between product complexity and time to approval, indicating that those two types of strategic alliances could lower the technical uncertainty and market uncertainty surrounding a new drug.

Our findings have important theoretical and practical implications. First, we extend the research on government-business relationships to the government side by considering product complexity and regulatory approval. The seminal work of Simonin (1999) tested the relationship between complexity and ambiguity in strategic alliances. As far as we know, no other research tests the characteristics of organizational output on the response from the regulatory agency. Our findings demonstrate that product complexity does have significant influences on the decision making of regulatory agencies. Second, our findings indicate that regulatory agencies are concerned about technical uncertainty. The characteristics of the focal firm shifts the concerns in different ways. Third, our study demonstrates the contingency effect of R&D alliance partners and marketing alliance partners in the regulatory approval process. Therefore, the relationship between product complexity and the time to approval is contextually dependent.

Although our theoretical predictions and empirical findings indicate that firms form strategic alliances to signal the high safety and market potential for the new drugs, focal firms are not necessarily expected to game the system. Previous research about "cheap talk" (Crawford & Sobel, 1982) and lying (e.g., Gneezy, Kajackaite, & Sobel, 2018) shows that it is unlikely for focal firms to form strategic alliances with an intention of misrepresentation or absent efficacy. Purposeful lying won't occur when there are significant costs associated with lying, such as tarnished reputation, damaged public image concern etc. (e.g., Abeler, Becker, & Falk, 2014; Dreber & Johannesson, 2008; Mazar, Amir, & Ariely, 2008). Gneezy, Kajackaite, and Sobel (2018) found that there are intrinsic costs associated with lying, depending on the magnitude of the lie. In new drug approval, focal firms usually make public announcement about strategic alliance partners. The public announcements would incur significant responses from shareholders and other important stakeholders (including judicial authorities) if these were misrepresentations. Moreover, the FDA review process could also guarantee the reliability of the new drugs, further decreasing the possibility of "cheap talk." Therefore, even though there is a possibility that the focal firm may send false signals (e.g., by lying about strategic alliance formation), the scrutiny by the public and the FDA will most likely alert stakeholders to these transgressions.

Our study is not without limitations which may offer the directions for future research. First, product complexity may have different effects on firm performance over time. For instance, complex products may take longer for the market to accept, leading to lower sales than less complex products at the initial stage of launch. However, at later stages, complex products may have more sales than less complex products due to the advantage in technology and safety. Therefore, future research could investigate how product complexity influences sales over time. Second, product similarity is another feature of the drug molecule which may interact with product complexity in affecting the decision of regulatory agency. Some products may be complex but similar to the products in other companies. Future research should address the effects product similarity has on regulatory approval. Third, due to the difficulty and availability of the data collection, FDA membership and philosophy was not well controlled in our empirical model. Future research may investigate the contingent factors from the FDA side about the relationship between product complexity and time to approval.

CONCLUSION

By taking a sample of drug molecules from pharmaceutical companies, we tested the association between product complexity and the time to approval by FDA. We find that there is a U-shaped relationship between product complexity and time to approval by FDA. We also find that the relationship between product complexity and the time to approval depends on the strategic alliances the focal firms have. We believe this study will provide new avenues for research in product complexity and offer more insights in the advancement of understanding about government-business relationship.

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REFERENCES

Abeler, J., Becker, A., & Falk, A. (2014). Representative evidence on lying costs. *Journal of Public Economics*, 113, 96-104.

Anderson, J. C., & Narus, J. A. (1990). A model of distributor firm and manufacturer firm working partnerships. *The Journal of Marketing*, 42-58.

Baldwin, C. Y., Clark, K. B. (2000). *Design Rules: The Power of Modularity*. MIT Press: Cambridge, MA.

Banker, R. D., Davis, G. B., Slaughter, S. A. (1998). Software development practices, software complexity, and software maintenance performance: a field study. *Management Science,* 44(4), 433–451.

Baum, J. A., Calabrese, T., & Silverman, B. S. (2000). Don't go it alone: Alliance network composition and startups' performance in Canadian biotechnology. *Strategic Management Journal*, 21(3), 267-294.

Bucklin, L. P., & Sengupta, S. (1993). Organizing successful co-marketing alliances. *The Journal of Marketing*, 32-46.

Caille, S., Cui, S., Faul, M. M., Mennen, S. M., Tedrow, J. S., & Walker, S. D. (2019). Molecular complexity as a driver for chemical process innovation in the pharmaceutical industry. *The Journal of Organic Chemistry*, 84(8), 4583-4603.

Carpenter, D. (2014). *Reputation and power: organizational image and pharmaceutical regulation at the FDA*. Princeton University Press.

Chan, T. Z. (2000). Beyond productivity in software maintenance: factors affecting lead time in servicing users' requests. *International Conference on Software Engineering Proceedings, October, San Jose, CA. Software Maintenance*. IEEE Computer Society: Los Alamitos, CA; 228–235.

Choi, J., & Contractor, F. J. (2016). Choosing an appropriate alliance governance mode: The role of institutional, cultural and geographical distance in international research & development (R&D) collaborations. *Journal of International Business Studies*, 47(2), 210-232.

Crawford, V. P., & Sobel, J. (1982). Strategic information transmission. *Econometrica: Journal of the Econometric Society*, 1431-1451.

Desai, V. M. (2016). Under the radar: Regulatory collaborations and their selective use to facilitate organizational compliance. *Academy of Management Journal*, 59(2), 636-657.

Diestre, L., & Rajagopalan, N. (2012). Are all 'sharks' dangerous? New biotechnology ventures and partner selection in R&D alliances. *Strategic Management Journal*, 33(10), 1115-1134.

Diestre, L., Rajagopalan, N., & Dutta, S. (2015). Constraints in acquiring and utilizing directors' experience: An empirical study of new-market entry in the pharmaceutical industry. *Strategic Management Journal*, 36(3), 339-359.

Dollinger, M. J., Golden, P. A., & Saxton, T. (1997). The effect of reputation on the decision to joint venture. *Strategic Management Journal*, 18(2), 127-140.

Dreber, A., & Johannesson, M. (2008). Gender differences in deception. *Economics Letters*, 99(1), 197-199.

Ethiraj, S. K., Ramasubbu, N., & Krishnan, M. S. (2012). Does complexity deter customer-focus?. *Strategic Management Journal*, 33(2), 137-161.

FDA. (2020). Coronavirus (COVID-19) Update: FDA Issues Emergency Use Authorization for Potential COVID-19 Treatment. https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-issues-emergency-use-authorization-potential-covid-19-treatment

Galambos, L., & Sturchio, J. L. (1998). Pharmaceutical firms and the transition to biotechnology: A study in strategic innovation. *The Business History Review*, 250-278.

George, G., Wiklund, J., & Zahra, S. A. (2005). Ownership and the internationalization of small firms. *Journal of Management*, 31(2), 210-233.

Geringer, J. M., Tallman, S., & Olsen, D. M. (2000). Product and international diversification among Japanese multinational firms. *Strategic Management Journal*, 21(1), 51-80.

Gerlach, M. L. (1992). The Japanese corporate network: A blockmodel analysis. *Administrative Science Quarterly*, 105-139.

Gneezy, U., Kajackaite, A., & Sobel, J. (2018). Lying Aversion and the Size of the Lie. *American Economic Review*, 108(2), 419-53.

Granovetter, M. (1985). Economic action and social structure: The problem of embeddedness. *American Journal of Sociology*, 91(3), 481-510.

Gulati, R., & Higgins, M. C. (2003). Which ties matter when? The contingent effects of interorganizational partnerships on IPO success. *Strategic Management Journal*, 24(2), 127-144.

Heese, J., Krishnan, R., & Moers, F. (2015). January. Regulator leniency and mispricing in beneficent nonprofits. In *Academy of Management Proceedings*, 2015 (1), 11998. Academy of Management.

Henderson, R. M., & Clark, K. B. (1990). Architectural innovation: the reconfiguration of existing product technologies and the failure of established firms. *Administrative Science Quarterly*, 9-30.

Hendrickson, J. B., Huang, P., & Toczko, A. G. (1987). Molecular complexity: a simplified formula adapted to individual atoms. *Journal of Chemical Information and Computer Sciences*, 27(2), 63-67.

Hiatt, S. R., & Park, S. (2013). Lords of the harvest: Third-party influence and regulatory approval of genetically modified organisms. *Academy of Management Journal*, 56(4), 923-944.

Hiatt, S. R., & Sine, W. D. (2014). Clear and present danger: Planning and new venture survival amid political and civil violence. *Strategic Management Journal*, 35(5), 773-785.

Hill, C. W. (1990). Cooperation, opportunism, and the invisible hand: Implications for transaction cost theory. *Academy of Management Review*, 15(3), 500-513.

Hoang, H., & Rothaermel, F. T. (2005). The effect of general and partner-specific alliance experience on joint R&D project performance. *Academy of Management Journal*, 48(2), 332-345.

Holmstrom, B. (1989). Agency costs and innovation. *Journal of Economic Behavior & Organization*, 12(3), 305-327.

Kogut, B., & Zander, U. (1993). Knowledge of the firm and the evolutionary theory of the multinational corporation. *Journal of International Business Studies*, 625-645.

Kozhikode, R. K. (2016). Dormancy as a Strategic Response to Detrimental Public Policy. *Organization Science*, 27(1), 189-206.

Leiblein, M. J., & Reuer, J. J. (2004). Building a foreign sales base: the roles of capabilities and alliances for entrepreneurial firms. *Journal of Business Venturing*, 19(2), 285-307.

Li, D., Eden, L., Hitt, M. A., & Ireland, R. D. (2008). Friends, acquaintances, or strangers? Partner selection in R&D alliances. *Academy of Management Journal*, 51(2), 315-334.

Mazar, N., Amir, O., & Ariely, D. (2008). The dishonesty of honest people: A theory of self-concept maintenance. *Journal of Marketing Research*, 45(6), 633-644.

Miller, C. C. & Cardinal, L. B. (1994). Strategic-planning and firm performance - a synthesis of more than 2 decades of research. *Academy of Management Journal*, 37(6): 1649-1665.

Munos, B. (2009). Lessons from 60 years of pharmaceutical innovation. *Nature Reviews Drug Discovery*, 8(12), 959-968

Neter, J., Wasserman, W., and Kutner, M. (1985). *Applied Linear Statistical Models*. Richard D. Irwin. Homewood, IL.

Novak, S., & Eppinger, S. D. (2001). Sourcing by design: product radicalness and the supply chain. *Management Science*, 47(1), 189-204.

Olausson, D., & Berggren, C. (2010). Managing uncertain, complex product development in high-tech firms: in search of controlled flexibility. *R&D Management*, 40(4), 383-399.

Oxley, J. E., & Sampson, R. C. (2004). The scope and governance of international R&D alliances. *Strategic Management Journal*, 25(8-9), 723-749.

Salomon, R. M., & Martin, X. (2003), August. Technology transfer and implementation: exploring the 'time-to-build' fabrication facilities in the global semiconductor industry. *In Academy of Management Proceedings* (Vol. 2003, No. 1, pp. J1-J6). Academy of Management.

Sampson, R. C. (2007). R&D alliances and firm performance: The impact of technological diversity and alliance organization on innovation. *Academy of Management Journal*, 50(2), 364-386.

Sanders, W. G. (2001). Behavioral responses of CEOs to stock ownership and stock option pay. *Academy of Management Journal*, 44(3), 477-492.

Saxton, T. (1997). The effects of partner and relationship characteristics on alliance outcomes. *Academy of Management Journal*, 40(2), 443-461.

Scillitoe, J. L., Gopalakrishnan, S., & Santoro, M. D. (2015). The impact of external contexts on alliance governance in biotech–pharmaceutical firm alliances. *Organization Management Journal*, 12(3), 110-122.

Shan, W., Walker, G., & Kogut, B. (1994). Interfirm cooperation and startup innovation in the biotechnology industry. *Strategic Management Journal*, 15(5), 387-394.

Simonin, B. L. (1999). Ambiguity and the process of knowledge transfer in strategic alliances. *Strategic Management Journal*, 20(7), 595-623.

Swaminathan, V. (2003). The impact of recommendation agents on consumer evaluation and choice: the moderating role of category risk, product radicalness, and consumer knowledge. *Journal of Consumer Psychology*, 13(1-2), 93-101.

Szulanski, G. (1996). Exploring internal stickiness: Impediments to the transfer of best practice within the firm. *Strategic Management Journal*, 17(S2), 27-43.

Tallman, S., & Li, J. (1996). Effects of international diversity and product diversity on the performance of multinational firms. *Academy of Management Journal*, 39(1), 179-196.

Tripathi, L., & Kumar, P. (2013). Designing of Novel 6 (H)-1, 3, 4-Thiadiazine Derivatives as MMP12 Inhibitors: A MLR and Docking Approach. *American Journal of Pharmacological Sciences*, 1(2), 29-34.

Walters, W.P., Green, J., Weiss, J.R. & Murcko, M.A. (2011). What do medicinal chemists actually make? A 50-year retrospective. *Journal of Medicinal Chemistry*, 54(19), 6405-6416.

Wernerfelt, B. 1984. A resource-based view of the firm. *Strategic Management Journal*, 5: 171-180.

Winter, S. G., & Szulanski, G. (2001). Replication as Strategy. *Organization Science* 12(6):730-743.

Wowak, A. J., Hambrick, D. C., & Henderson, A. D. (2011). Do CEOs encounter within-tenure settling up? A multiperiod perspective on executive pay and dismissal. A*cademy of Management Journal*, 54(4), 719-739.

Yap, C. W. (2011). PaDEL-descriptor: An open source software to calculate molecular descriptors and fingerprints. *Journal of Computational Chemistry*, 32(7), 1466-1474.

Zhang, Y., Li, H. Y., Hitt, M. A., & Cui, G. (2007). R&D intensity and international joint venture performance in an emerging market: Moderating effects of market focus and ownership structure. *Journal of International Business Studies*, 38(6): 944-960.