Drug Pipelines and Pharmaceutical Licensing

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Abstract

We examine how drug pipelines (drug candidates and post-market product lines) affect pharmaceutical licenses, controlling firm size, diversity, and competition. The data collected comprises 347 license-outs and 604 license-ins closed by 54 Japanese pharmaceutical companies between 1997 and 2007. We classify licensing contracts into four stages: (i) drug discovery, (ii) early development, (iii) late development, and (iv) marketing. Estimates from random effect IV models reveal that fewer drug candidates in either late development or marketing stages accelerate license-ins in various stages. On the other hand, richer pipelines in any stage facilitate license-outs in that stage. In addition, theoretical implications are discussed.

JEL classification: C13; L24; L65.

1. Introduction

Understanding the mechanism of the technology market enables us to enhance the rate of return on research and development (R&D) through the outsourcing of knowledge across a firm's boundary (Penrose, 1959; Williamson, 1985). There are two effects of license-out on profit: (i) *revenue effect* (rents earned by the licensor in the form of royalty) and (ii) *rent dissipation effect* (the erosion of profits due to competition of the licensee). A majority of previous studies on the technology market examine the manner in which complementary assets affect licensing propensity (Teece, 1986; Cohen Levinthal, 1989, 1990; Arora et al. 2001; Shane, 2001; Arora and Fosfuri, 2003; Kollmer and Dowling, 2004; Arora and Ceccagnoli, 2006; Fosfuri, 2006).

However, there are few empirical studies that explore the effect of R&D portfolio on licensing. This paper examines the manner in which R&D portfolios, which is reflected in *drug pipelines* of pharmaceutical firms (product lines and drug candidates under development stages), influence the activity of inward and outward licensing, controlling firm size, diversity, and the degree of competition at either the drug development or product market stage.

In a recent theoretical study, Chan et al (2007) provided a model of project selection that explicitly incorporates R&D pipelines, transaction costs, and downstream *co-specialized assets* (Williamson 1985) such as distribution channels and brands. By using a dynamic programming technique, they examined the investment and licensing decisions. They indicate that the state of R&D pipelines and the existence of downstream co-specialized assets affect the optimal R&D portfolio as well as incentive to use the technology market at different R&D stages. For example, research-oriented firms with no downstream complementary assets are likely to sell their research outcomes to downstream licensees.

Accordingly, we expect that pharmaceutical firms with fewer drug candidates are likely to outsource external seeds at a later stage, while research-oriented firms with no downstream assets are not likely to buy drug candidates[1] at a later stage. On the other hand, we suspect that richer pipelines in a certain stage facilitate license-outs in that stage,

[1] In similar vein, Higgins and Rodriguez (2006) and Danzon et al. (2007) explore the incentive for mergers and acquisitions (M&A) in the U.S. pharmaceutical industry as a method to obtain external R&D outcomes.

although the rent dissipation effect aggravates the incentive to license out to firms with downstream complementary assets.

The data we collected comprises 347 license-outs and 604 license-ins closed by 54 Japanese pharmaceutical companies between 1997 and 2007 with various types of counterparts such as horizontal rivals, bio-ventures, and universities. Furthermore, we define a portfolio of drug pipelines and classify the process of pharmaceutical R&D into four stages: (i) drug discovery, (ii) early development, (iii) late development, and (iv) marketing.

Estimates from random effect IV models reveal that fewer drug candidates in either the late development or marketing stage accelerate license-ins in various stages. On the other hand, richer pipelines in any stage facilitate license-outs in that stage. Thus, we find a significant R&D portfolio effect on licensing, as theoretically indicated by Chen et al. (2007). Moreover, we find that pharmaceutical firms with larger sales are more likely to introduce external drug seeds at any stage, although they are not likely to license out at all stages except marketing. Arguably, the propensity to license-in may be strengthened by downstream complementary assets, whereas the propensity to license-out may be weakened by the rent dissipation effect.

This paper is organized as follows. In the next section, we indicate the trend of pharmaceutical licensing and present the classification of licensing stages and drug pipelines. In section 3, we overview the theoretical background and propose our hypotheses. In section 4, we explain variable construction and the empirical model. In section 5, we present the empirical results. In section 6, we conclude our findings.

2. Pharmaceutical licensing in Japan

2.1. Trend of pharmaceutical licensing

Figure 1 presents the trend of pharmaceutical licensing in Japan from 1997 to 2007[2]. The number of license-ins and license-outs fluctuated virtually in a similar manner. However the number of license-ins always exceeds that of license-outs, and increased steeply between 2000 and 2002. During this period, Japanese pharmaceutical firms are indicated as being rather active in terms of inward licensing from bio-ventures and other pharmaceutical firms[3]. This may partially reflect the laggard introduction of molecular biology in pharmaceutical R&D in Japan (Henderson et al. 1999).

2.2. Drug pipelines and licensing stages

New drug development is a sequential process. Figure 2 presents the typical process of pharmaceutical R&D. Quite a few drug candidates at the *discovery* stage will be screened for synthesis by chemists and biologists in order to develop concepts for new compounds. Once a new compound has been synthesized, it will be screened for pharmacologic activity and toxicity in vitro and animals (*pre-clinical* testing), and thereafter in humans.

Human clinical testing typically comprises three distinct stages, i.e., *phase I*, *phase II*, and *phase III*, each of which involves different types of testing on safety and efficacy. Phase I is performed on a small number of healthy human subjects in order to obtain information on toxicity and safe dosage ranges. Phase II is performed on a larger number of humans who are patients for whom the drug is intended to be prescribed. Phase III involves large-scale trials on patients. The later a clinical trial is conducted, the greater its cost. Therefore, it is rather important for a pharmaceutical firm to screen promising seeds as efficiently as possible (DiMasi et al., 2003). Finally, a pharmaceutical firm will submit the drug candidate that passes phase III to the Ministry of Health, Labor and Welfare (MHLW), and an approved drug is brought to the market after registration with MHLW.

It is rather probable that a large pharmaceutical firm has at least one drug candidate at almost every stage, while it is rather likely that a smaller firm has no drug candidates at certain stages. In order to examine the manner in which a drug portfolio affects licensing decisions of various types of pharmaceutical firms, we divide drug candidates into the

[2] Data sources are explained in Appendix A.
[3] Ohkubo (2008) explained the trend of pharmaceutical licensing in Japan.

following three categories: (i) *early development*, (ii) *late development*, and (iii) *marketing*. Since clinical testing on patients in phases II and III is much more costly than in pre-clinical and phase I, we divide the development stage into the early and late development stages, as shown in Figure 2. The early development stage comprises pre-clinical and phase I, whereas the late development stage comprises phases II and III. Under such a slightly rough classification, we are able to examine the stage-specific incentive to license with sufficient observations for each stage. Although we do not have information on the number of drug seeds at the discovery stage due to data constraints, we can identify the number of licensing contracts at the discovery as well as the development stages.

2.3. Stage-specific pharmaceutical licensing

Table 1 presents the stage-specific licensing activities and drug pipelines of 54 Japanese pharmaceutical firms for the years 1997–2007. The number of license-ins and license-outs are classified by firm size (i.e., drug sales) in 2005. Note that since several firms underwent mergers and acquisitions (M&A) in 2005, the total number of firms as of 2005 is 41.

Table 1 presents the salient characteristics of pharmaceutical licensing that are worth noting. First, larger firms are more likely to license in. Over one-third of total inward licensing is conducted by large pharmaceutical firms with drug sales of over 500 billion, and annual average license-ins per firm (3.59) is much higher than that in other smaller size categories. Second, it appears that richer pipelines in the initial development stage may facilitate licensing-out at that stage. On the other hand, the number of drug candidates at the late development stage appears to have no relationship with outward licensing. Third, it is likely that richer pipelines at every stage facilitate inward licensing. Finally, the number of license-outs at the discovery stage is 18, which is much smaller than those at other stages. This may be due to missing observations. Therefore, the incentive to license out must be carefully examined at the discovery stage.

3. Hypotheses formulation

This section explains our hypotheses regarding the relationship between licensing and the state of drug pipelines, controlling firm size, therapeutic diversity, and market competition.

3.1. Drug pipelines and licensing

As indicated by Chan et al (2007), we expect that pharmaceutical firms with fewer drug candidates at a later stage are likely to outsource external drug seeds at that stage, while research-oriented firms with no downstream assets are not likely to insource drug candidates at a later stage. On the other hand, we assume that richer pipelines in a certain stage facilitate license-outs at that stage. Therefore, we formulated the following hypothesis:

Hypothesis 1: Richer drug pipelines at any stage of pharmaceutical R&D facilitate license-outs at that stage.

Hypothesis 2: Fewer drug pipelines at either the late development or market stage accelerate license-ins.

Hypothesis 1 implies that firms with richer drug pipelines at any stage can exploit in-house seeds by outward licensing, i.e., revenue effect facilitates license-outs. On the other hand, firms may be reluctant to license out at the late development stage due to the rent dissipation effect. Namely, license-outs at the late development stage may intensify product market competition in the future.

Hypothesis 2 implies that pharmaceutical firms with fewer drug candidates at either the late development or market stages have to maintain downstream assets (such as statisticians, collaborative network with physicians, and medical representatives) by replenishing external drug seeds at the late development stage.

There are very few empirical studies that examine the relationship between R&D pipelines and licensing. However, in a recent interesting study, Higgins and Rodriguez (2006) evaluated the state of R&D portfolios and found that firms with thin R&D pipelines are more likely to be engaged in M&A. M&A and license-in can be regarded as complementary strategies for introducing external knowledge, although recently there

have been quite a few merger cases in the Japanese pharmaceutical industry.

3.2. Firm size and outward licensing

Arora and Fosfuri (2003) developed a model that demonstrates that firms conduct license-outs when the revenue effect (rents earned by the licensor in the form of royalty) is higher than the rent dissipation effect (the erosion of profits due to licensee's competition). Their model indicates that the rent dissipation effect becomes smaller if the licensor has a small market share because the licensor suffers a lower loss from generating competitors. In similar vein, Fosfuri (2006) indicates that firms with large market shares do not tend to license out.

There are numerous factors that influence the extent of revenue and/or rent dissipation effect. For example, a large transaction cost causes a smaller revenue effect and makes license-out a less attractive strategy (Teece, 1986). Stronger patent protection may raise the revenue effect. Furthermore, the rent dissipation effect becomes smaller if the market of a licensee is strongly segmented from that of a licensor.

Teece (1986) discusses the role of complementary assets to reduce the propensity to license out. A broad range of empirical literature suggests that a large vertically integrated firm that owns downstream complementary assets is reluctant to license out. For example, Shane (2001), Kollmer and Dowling (2004), Ohnishi and Okada (2005), Arora and Ceccagnoli (2006), Motohashi (2006), and Gambardella et al (2007), among others, provide evidence that is consistent with Teece (1986). These studies lead us to formulate the following hypothesis.

Hypothesis 3: Larger firms are less likely to license out internal drug seeds.

Contrary to Hypothesis 3, it may be also possible that larger firms are willing to license out their internal technologies. As argued by Gallini (1984), a dominant firm may strategically license out its technologies in order to prevent competitors from developing better technologies. Rockett (1990) developed a similar argument that a large firm licenses out its technologies to a weak rival in order to crowd out other stronger competitors. Furthermore, Kim (2004) suggested that a larger firm may not be worried with regard to an increase in competitors because of its dominant market position. In similar vein, Nakamura and Odagiri (2005), Kim and Vonortas (2006), and Nagaoka and

Kwon (2006) suggested that larger firms are more likely to be involved in license-outs.

Thus, there are no robust findings regarding the relationship between firm size and propensity for outward licensing. Hypothesis 3 continues to be an important empirical question that must be examined.

3.3. Firm size and inward licensing

With regard to the relationship between firm size and license-ins, Cohen and Levinthal (1989, 1990) convincingly argued that large firms have greater absorptive capacity to assimilate and exploit existing outside information. Moreover, Fosfuri (2006) argue that larger firms have greater bargaining power over smaller firms in negotiating licensing conditions. Nakamura and Odagiri (2005) find that larger firms are likely to license in, and indicate that firm size as a proxy for organizational capability is positively associated with the value of license-ins. This argument may be verified in the form of the following hypothesis.

Hypothesis 4: Larger firms are more likely to license in external drug seeds.

3.4. Therapeutic Diversity

Pharmaceutical firms dealing with a large number of therapeutic fields may have better organizational capability to assimilate external knowledge. Specifically, co-specialized assets used in R&D, manufacturing, and marketing may be an important source of scope economies (Henderson and Cockburn 1996; Cohen and Levinthal 1989, 1990). Therefore, it will be much easier for more diversified firms to assimilate a wide range of external knowledge. Thus, we present the following hypothesis:

Hypothesis 5: Firms with diverse therapeutic fields are likely to license in.

On the other hand, as far as we know, there are no solid theoretical predictions as well as empirical findings regarding the relationship between therapeutic diversity and outward licensing. Therefore, we additionally hypothesize that firm diversity may have some positive impact on license-outs.

Hypothesis 6: Firms with diverse therapeutic fields are likely to license out.

This may happen because of various reasons. For example, it may be much easier for diversified firms to find licensee partners (as well as licensors), as in a random matching game. Furthermore, internal resource constraints would raise the opportunity cost of in-house R&D and enhance the revenue effect of exploiting internal knowledge through license-outs. In order to further examine these possibilities, we require additional information regarding a combination of a licensor and licensee. Unfortunately, this type of data is not available in the present study.

3.5. Market competition

The degree of competition at either the development or the marketing stage may have a significant impact on licensing decisions. Arora and Fosfuri (2003) indicate that outward licensing is less likely if there are few competitors in R&D, other things being equal. For example, R&D competition may raise the profitability of license-outs. If there are a large number of rivals in R&D, it is rather difficult to appropriate the outcome of R&D by a single firm. Similarly, Arora and Fosfuri (2003) indicate that product market competition also facilitates outward licensing because a large number of competitors in a product market make it difficult to appropriate the R&D outcome in a product market. In other words, the revenue effect tends to overcome the rent dissipation effect when there are a greater number of competitors. This consideration produces the following hypothesis.

Hypothesis 7: Market competition is likely to increase the incentive to license out.

We will define the extent of competition across therapeutic categories in detail in the next section. Recent empirical studies demonstrated the significant role of competition in the technology and product markets. For example, Fosfuri (2006) and Kim and Vonotras (2006) indicate that competition stimulates outward licensing using competition indices such as the number of potential licensors (Fosfuri, 2006) and four-firm concentration ratio (Kim and Vonotras, 2006).

On the other hand, there are no empirical studies examining the competition effect on inward licensing. Market competition may have some positive impact on license-in. Fierce competition, particularly at a later stage, would make it difficult for a pharmaceutical firm to retain sufficient cash-flow to maintain R&D investment. Thus, we put forward the following hypothesis:

Hypothesis 8: Market competition is likely to increase the incentive to license in.

As indicated in Figure 1, Japanese pharmaceutical firms actively contracted license-ins between 2000 and 2002. This may have been because of the prospect of severe market competition and exhaustion of drug pipelines in the near future.

4. Empirical analysis

Table 2 summarizes variable definitions and basic statistics. In this section, we will first explain variable constructions of dependent and independent variables. Then, we will present empirical specifications.

4.1. Dependent variable: Outward and inward licensing

The variable *in_total* is the total number of license-ins at all stages. We also define the variables *in_discovery*, *in_early*, *in_late*, and *in_market* as the number of license-ins at a corresponding stage of the R&D process. Similarly, we construct the dependent variables for license-outs as *out_total*, *out_discovery*, *out_early*, *out_late*, and *out_market*.

Furthermore, we will redefine these dependent variables as a binary value in a probit type specification. In other words, if a firm enters into a license contract, the dependent variable takes on the value of unity, and zero otherwise.

4.2. Independent variable

Drug pipelines

The variables *p_total*, *p_early*, *p_late*, or *p_market* denote the number of drug candidates at the corresponding stage.

Firm size

We employ the variable *sales* (drug sales) as a proxy for firm size and complementary assets. We use Corporate Goods Price Index (CGPI) given by the Bank of Japan as a deflator of drug sales.

Therapeutic diversity

The variable *scope* is the diversity index of sales. We classified drug sales into 16 therapeutic fields according to the *Anatomical Therapeutic Classification* (ATC)[4]. We first calculated the Herfindahl index H based on the sales share of each firm and created the diversity index as $1/H$.[5]

[4] See Appendix A in detail.
[5] See Appendix B in detail.

Market competition

We construct two types of competition index according to the development stage and product market. Unfortunately we have no information on the therapeutic category of drug seeds for each licensing contract. Considering this data restriction, we construct the Herfindahl index weighted by drug sales in ATC sub-markets at the development or marketing stage denoted by the variables *comp_develop* or *comp_market*, respectively.[6]

Other control variables

Further, we introduce two control variables, sales growth (*sales_growth*) and year dummies (*d_year*), in accordance with Fosfuri (2006).

4.3. Empirical specification

Using firm-year panel data, we employ probit and panel tobit regressions taking into consideration a large number of zero values of dependent variables. In addition, we conduct logit and negative binomial regressions for the sole purpose of conducting a robustness check[7]. The regressions support random effect models according to Hausman specification tests. The basic specification of a random effect probit model is as follows.

$$Y_{it}^{*} = \beta X_{it} + \varepsilon_{it} \quad \varepsilon_{it} \sim \mathrm{N}(0, 1),$$
$$Y_{it} = 1 \text{ if } Y_{it}^{*} > 0, \text{ and}$$
$$Y_{it} = 0 \text{ otherwise,}$$

where *i* denotes firm and t denotes year. X includes the independent variables explained in the previous section. The variable Y_{it}^{*} is a latent variable that represents an unobservable index of ability or desire on the part of pharmaceutical firm *i* to license out or in with alliance partners at time *t*. If the measure is positive, we assume that Y_{it} takes on the positive value of one. We consider the random effect model on the composite error term in the following manner:

[6] See Appendix B in detail.

[7] The results of alternative estimations are not considerably different from basic empirical results. Therefore, we only provide the estimation results of panel probit and tobit.

$$\varepsilon_{it} = v_{it} + e_i, \qquad Var[\varepsilon_{it}] = \sigma_v^2 + \sigma_e^2, \qquad Corr[\varepsilon_{it}, \varepsilon_{is}] = \rho = \sigma_v \sigma_e .$$

We suppose that v_{it} and e_i are independent and identically distributed. If the correlation ρ is zero, it may be possible to run a pooled probit regression. However, according to the LM-test, estimates in various specifications support the random effect model at least at the 5% significance level. Thus, our empirical specification is

$$\begin{aligned} license_{it}^{s} = {} & \beta_1 pipeline_{it}^{s} + \beta_2 sales_{it} + \beta_3 sales\_growth_{it} + \beta_4 scope_{it} \\ & + \beta_5 comp\_develop_{it} + \beta_6 comp\_market_{it} + \sum \delta d\_year + \varepsilon_{it} . \end{aligned}$$

The superscript *s* represents the distinct stage of license activity and/or drug pipelines, as described in Section 2.

4.4. Endogeneity issue

There may be a serious endogeneity problem of reverse causality with regard to drug pipelines because drug pipelines influencing a firm's license activity are themselves influenced by a firm's license activity. In order to cope with this endogeneity problem and check the robustness of our basic model, we further estimate the random effect instrumental variable and bivariate probit models.

First, we conduct a 2SLS (IV) estimation. This can be done by obtaining the predicted values of drug pipelines, regressing against the instrumental variable that is correlated with drug pipelines but exogenous to the dependent variable. We use one-year lagged variables of drug pipelines as the instrumentals because they are assuredly correlated with present drug pipelines but are not likely to be correlated with present licensing decisions.

Next, firms may conduct licensing at some stage taking into consideration the pipelines of other stages. In this case, the disturbances do not satisfy the i.i.d. condition. In order to control this endogeneity problem, we conduct a bivariate probit model where two different arbitrary dependent variables are permitted to be correlated with each other. In our unreported work, we obtained virtually similar results to the random effect probit and tobit regressions. Thus, we will only report the estimation results of probit, tobit, and 2SLS (IV) regressions in the next section.

5. Estimation results

5.1. Determinants of license-outs

First, we employ regressions with the total number of outward licensing (*out_total*) as a dependent variable. Table 3 presents the estimation results of random effect probit, random effect tobit, and random effect IV regressions. We use *p_total*, *sales*, *sales_growth*, *scope*, *comp_develop*, *comp_market*, and *d_year* as independent variables. The results indicate that all the coefficients of *p_total* are significantly positive at the 1% or 5% significance level. This is consistent with *Hypothesis 1*.

Several other independent variables are also significant. First, the coefficient of *sales* is significantly negative at the 10% significance level. Although the significance level is rather weak, this may indicate that the rent dissipation effect dominates the revenue effect, as is expected from *Hypothesis 3*.[8] This result is consistent with Fosfuri (2006) and Arora and Ceccagnoli (2006). However, it must be noted that our sample comprises relatively large pharmaceutical firms with downstream complementary assets. This feature of our dataset may affect the likelihood of drug seeds being exploited in-house.

With regard to therapeutic diversity, the relevant variable *scope* is significantly positive at the 5%–10% level. This positive coefficient is consistent with *Hypothesis 6*. It may be easier for a pharmaceutical firm with drug candidates across diverse therapeutic fields to find potential licensees.

Finally, the coefficient of *comp_develop* is positive and strongly significant. It would be difficult to keep technologies secret if there are numerous competitors and potential licensors at the development stage. Thus, the expected return of a drug seed in the future may become lower and pharmaceutical firms are more likely to license their technologies out in order to obtain license royalties (Arora and Fosfuri, 2003). This result is consistent with *Hypothesis 7*.

Stage-specific propensity to license out

Table 4 summarizes the results of stage-specific determinants of license-outs. We

[8] There may be multicollinearity between *sales* and drug pipelines, particularly at the market stage. However, even if we exclude either one of these variables, the estimation results are virtually the same as those of our basic model.

employed regressions stage by stage. The dependent variable is *out_discovery*, *out_early*, *out_late*, or *out_market*. We use the information on drug pipelines as independent variables with three distinct stages *p_early*, *p_late*, and *p_market*. Other independent variables are the same as those given in Table 3. The main estimation results are summarized as follows.

First, the coefficients of *p_early* and *p_late* are significantly positive at the discovery stage in all specifications. If the relevant technologies in the discovery stage are general-purpose, the potential number of licensees may be larger and expected revenues from license-outs are higher. In this case, it is more attractive for licensors to sell their technologies than keep these technologies in-house (Gambardella et al., 2007).

Second, the coefficient of *p_early* is significant and positive in the early development stage. Similarly, the coefficient of *p_market* is positive and significant in the market stage. These results suggest that the incentive to stage-specific license out depends on the corresponding number of in-house drug seeds.

However, the coefficient of *p_late* is not significant in all specifications. As is expected from the summary statistics in Table 1, there is no clear relationship between license-outs and drug pipelines in the late development stage. Pharmaceutical firms may be reluctant to license out at that stage even if they have numerous drug candidates because they expect higher revenues *ex post* in the late development stage through in-house development and it is also advantageous to maintain downstream complementary assets.

Third, the coefficient of *comp_develop* is significantly positive at both the early and late development stages, whereas it is significantly negative at the marketing stage. In other words, pharmaceutical firms that face severe competition at the development stage are more likely to license out at the development stage. On the other hand, at the marketing stage, pharmaceutical firms hesitate to license out their post-market products if they face severe competition at the development stage.

The following are the possible reasons for the salient results with regard to the variable *comp_develop*. First, it is difficult for pharmaceutical firms that are facing fierce development competition to keep technologies secret. Therefore, they want to introduce their drug candidates into the product market as soon as possible (Arora and Fosfuri, 2003). On the other hand, under fierce development competition, pharmaceutical firms

may expect that potential competitors will enter the market in the near future. Therefore, they expect that the rent dissipation effect is heightened by license-outs at the marketing stage.

5.2. Determinants of license-ins

First, we employ regressions with the total number of inward licensing (*in_total*) as a dependent variable. Table 5 presents the estimation results of random effect probit, random effect tobit, and random effect IV regressions. We use *p_total*, *sales*, *sales_growth*, *scope*, *comp_develop*, *comp_market*, and *d_year* as independent variables.

The coefficient of *p_total* is negative but not significant in both the tobit and probit models. However, it is negative and significant at the 5% level in the random effect IV regression. This implies that firms with fewer drug pipelines tend to accelerate license-ins. This result supports *Hypothesis 2*.

The coefficients of *sales* and *scope* are significantly positive at the 1% or 5% level. These results support *Hypotheses 4 and 5*. Firms with greater capacity of R&D, manufacturing, and marketing are able to absorb external resources more easily, which enable such firms to be more likely to license in. This result is consistent with the empirical results in Nakamura and Odagiri (2005).

Finally, the coefficient of *comp_develop* is negative; however, the significance level is rather low in the tobit and probit models. This may imply that firms that face severe competition at the development stage do not have a tendency to license in. However, this variable is no longer significant in the random effect IV model. These results are inconsistent with *Hypothesis 8*. Thus, we do not have any robust results regarding the relationship between market competition and license-ins.

Stage-specific propensity to license in

Table 6 summarizes the results of stage-specific determinants of license-ins. The dependent variables are *in_discovery*, *in_early*, *in_late*, or *in_market*. The independent variables are the same as those provided in Table 4.

The estimation results of the tobit and probit models indicate that the coefficients of drug pipelines are not significant in a majority of the cases. However, the results in the random effect IV model partially support *Hypothesis 2*. Hereafter, we focus on the

random effect IV results.

First, the coefficient of *p_late* is weakly significant and negative at either the late development or marketing stage. In other words, firms with fewer drug candidates at the late development stage are more likely to license in at either the late development or marketing stage.

Second, the coefficient of *p_market* is significantly negative at both the discovery and early development stages. Hence, firms with fewer drug seeds at the marketing stage tend to license in at either the discovery or early development stage.

Third, the coefficient of *p_early* is unexpectedly positive and significant at the marketing stage. This is inconsistent with *Hypothesis 2*. However, in order to convincingly interpret this result, there are numerous missing links between the drug seeds at the early stage and the propensity to license in at the marketing stage that must be established.

Fourth, the coefficient of *sales* is significantly positive at the 1% or 5% level. Thus, *Hypotheses 4* is strongly supported.

Finally, the coefficient of *comp_market* is significantly positive at the late development stage. This suggests that firms facing severe market competition are more likely to license in at the late development stage. This is consistent with *Hypothesis 8*. On the other hand, the coefficient of *comp_develop* is significantly negative at the marketing stage. This is inconsistent with *Hypothesis 8*. In order to interpret these results, the comparison with the estimates of license-out may be useful. As indicated in Table 4, tougher competition at the development stage reduces the number of both license-outs as well as license-ins at the marketing stage. This symmetric evidence suggests that the rent dissipation effect deters inward as well as outward licensing at the marketing stage.

6. Conclusion

The present paper examines the manner in which drug pipelines affect pharmaceutical licenses. As is consistent with theoretical literature, we find that the state of drug pipelines significantly affects licensing decisions.

Several implications have been derived in this paper. First, license-in and license-out are differently affected by the state of drug pipelines. Roughly speaking, we found *within-stage* interactions between pipelines and license-outs, particularly at the early development and marketing stages. On the other hand, *across-stage* interactions between pipelines and license-ins are observed, particularly at the late development and marketing stages.

Second, firm size, therapeutic diversity, and market competition are also related with licensing decisions. It is more important for organizational capability to be related with inward licensing, while rent dissipation effect is more relevant to outward licensing.

This paper has several limitations. First, our dataset mainly includes licensing contracts with drug candidates. We do not have sufficient information on the licensing of research tools such as biotechnologies. This may underestimate the significant role of technology licensing in the pharmaceutical industry.

Second, the present study does not consider the value of licensing contracts. The value of each drug candidate differs significantly according to the relevant stage of the R&D process. However, changing features of option values at different stages would complicate further exploration. Patent statistics could offer possible clues for examining the option values of drug candidates.

Finally, we consider both aspects of license-in and license-out at the same time. However, we do not analyze the pairwise controls of the characteristics of licensors and licensees, as is done by Kim and Vonotras (2006), mainly due to data restriction. This requires broader and more comprehensive data collection, although information on pharmaceutical licensing is generally difficult to obtain because of the strong propensity to secrecy among pharmaceutical firms, particularly in Japan. Any further analysis must take these limitations into consideration.

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Appendix A
Data Sources

Our data comprises three data sets: license-outs and license-ins, drug pipelines, and firm characteristics. First, we select 54 pharmaceutical firms that participate in the Japan Pharmaceutical Manufacturers Association (JPMA). JPMA is a voluntary organization of research-based pharmaceutical manufacturers that has 69 members as of October 1, 2008. From among 69 firms, we exclude 15 firms that are foreign-affiliated and whose main business is generic drug, medical device, or Chinese herbal medicine. Certain firms in our sample underwent M&A. Thus, we obtain firm characteristics at the time when licensing contracts are awarded.

Next, we investigated the license activity of these 54 firms through the websites of each company, financial reports, and *Asuno Shinyaku* (the database of drug developments and alliances of firms). As a result, we collected 347 license-out and 604 license-in contracts with various types of counterparts such as horizontal rivals, biotechs, and universities between 1997 and 2007. The data on license-outs and license-ins is categorized into four stages of pharmaceutical R&D process, as discussed in section 2.2.

Second, we collect the information on the drug pipelines of 54 firms. Drug pipeline data is gathered through *Pharmaprojects*, the database by Informa UK Ltd. Drug pipelines are also classified into three stages. Moreover, drug pipelines can be divided into 16 therapeutic fields by the Anatomical Therapeutic Classification (ATC) prepared by the European Pharmaceutical Market Research Association: 1) Alimentary T.& Metabolism, 2) Blood & B.Forming Organs, 3) Cardiovascular System, 4) Dermatologicals, 5) G.U.System & Sex Hormones, 6) Systemic Hormones, 7) Systemic Anti-Infectives, 8) Hospital Solutions, 9) Antineoplast & Immunomodul, 10) Musculo-Skeletal System, 11) Central Nervous System, 12) Parasitology, 13) Respiratory System, 14) Sensory Organs, 15) Diagnostic Agents, and 16) Various.

Finally, we collect and construct firm characteristics such as size and therapeutic diversity. We use drug sales as a proxy for firm size derived from *Katsudou Gaikyou Chousa* (the annual questionnaire survey by JPMA). We also collect sales data in 16 therapeutic fields by ATC from IMS World Review (IMS Health). Using this data, we calculate the inverse of Herfindahl index of sales share and construct the therapeutic diversity and competition index of firms.

Appendix B

Variable construction on therapeutic diversity and market competition

Therapeutic diversity

We calculate sales share T_{ikt} in each of the 16 therapeutic fields of ATC.

$$\sum_k T_{ikt} = 1 \ ,$$

where *k* represents therapeutic fields (1, 2, …K), *i* is firm (1, 2, … N), and *t* is year. Then, we construct the therapeutic diversity *scope* of the firm as follows.

$$\sum_k T_{ikt}^2 = H_{it} \ , \ scope_{it} = \frac{1}{H_{it}} \ .$$

Market competition

We first calculate sales share S_{ikt} in each of the 16 therapeutic fields of ATC.

$$\sum_i S_{ikt} = 1 \ ,$$

where *k* represents therapeutic fields (1, 2, …K), *i* is firm (1, 2, … N), and *t* is year. The sales data in each therapeutic field of all firms in the pharmaceutical industry are derived from IMS World Review (IMS Health). Thereafter, we create the diversity index D_{kt} in each therapeutic field through the Herfindahl index B_{kt}.

$$\sum_i S_{ikt}^2 = B_{kt} \ , \ D_{kt} = \frac{1}{B_{kt}} \ .$$

Finally, we can obtain the competition index in the product market *comp_market* based on these indexes. We normalize sales share S_{ikt} and diversity index D_{kt} by subtracting their average from raw data.

$$comp\_market_{it} = \sum_k (S_{ikt} - \overline{S}_{kt})(D_{kt} - \overline{D}_t) \quad \frac{1}{N}\sum_i S_{ikt} = \overline{S}_{kt} \quad \frac{1}{K}\sum_k D_{kt} = \overline{D}_t \ .$$

Thus, this competition index is the Herfindahl index weighted by drug sales in ATC

sub-markets. By calculating S_{ikt} by the share of drug pipelines at development stages, we also obtain the competition index at the development stage *comp_develop*.

Figures and Tables

Figure 1: Division of licensing and drug pipeline stages

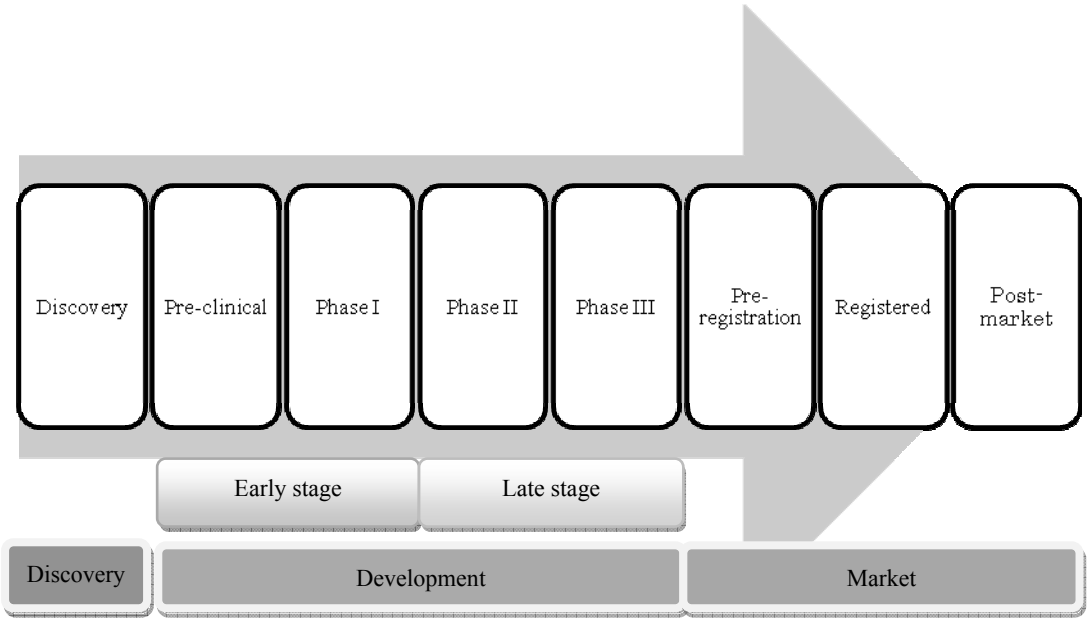
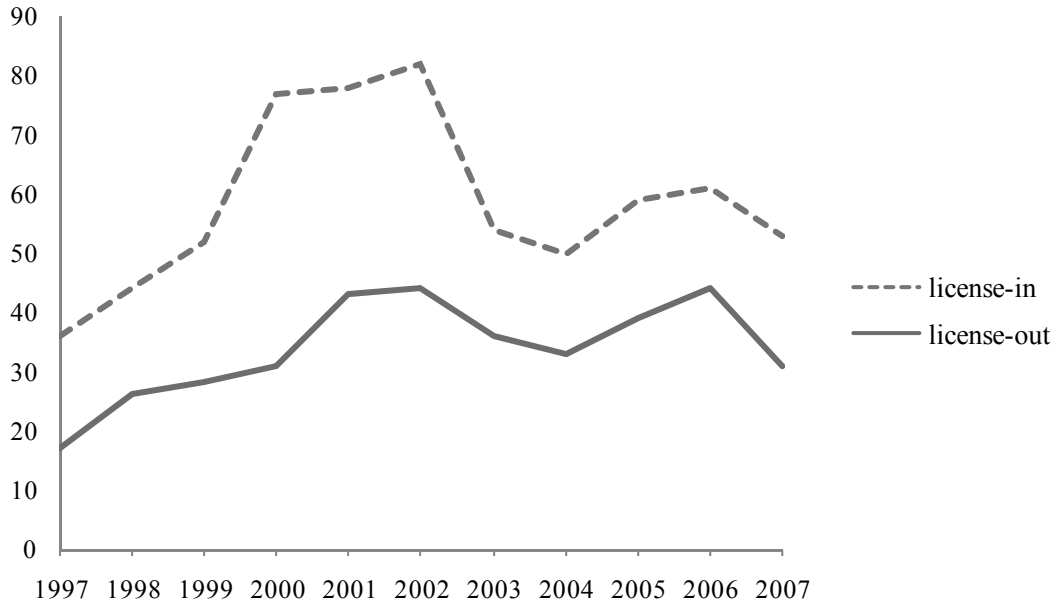


Figure 2: Trend of licensing by pharmaceutical firms in Japan



Data source: See Appendix A

Table 1: Stage-specific licensing and drug pipelines

Firm size		License-ins					License-outs					Drug pipelines			
Drug sales (billion yen)	Number of firms	total	discovery	early	late	market	total	discovery	early	late	market	total	early	late	market
sales≧500	4	224 (3.59)	87 (1.40)	53 (0.85)	29 (0.46)	55 (0.88)	52 (0.83)	3 (0.05)	15 (0.24)	8 (0.12)	26 (0.41)	4534 (73.12)	941 (15.17)	881 (14.20)	2712 (43.74)
500＞sales＞100	10	137 (1.05)	41 (0.31)	48 (0.36)	18 (0.13)	30 (0.23)	121 (0.93)	7 (0.05)	52 (0.40)	24 (0.18)	38 (0.30)	5143 (39.56)	948 (7.29)	1023 (7.86)	3172 (24.40)
100≧sales	27	243 (0.72)	38 (0.11)	96 (0.29)	32 (0.09)	77 (0.23)	174 (0.52)	8 (0.02)	76 (0.23)	37 (0.11)	53 (0.16)	5337 (16.07)	1124 (3.38)	1118 (3.36)	3095 (9.32)
Total	41	604 (1.15)	166 (0.32)	197 (0.37)	79 (0.15)	162 (0.31)	347 (0.66)	18 (0.03)	143 (0.27)	69 (0.13)	117 (0.22)	15014 (28.65)	3013 (5.75)	3022 (5.76)	8979 (17.13)

Note 1: Firms are classified by drug sales as of 2005.
Note 2: Annual average number of licensing and drug pipelines is given in parenthesis.
Data source: See Appendix A.

Table 2: Definition and basic statistics of variables (units: 54 firms, year: 1997–2007)

Variable	definition	Obs	Mean	Std. Dev.	Min	Max
License-outs	Number of outward licensing					
out_total	Total number	524	0.66	0.98	0	5
out_discovery	Drug discovery stage	524	0.03	0.21	0	2
out_early	Early development stage	524	0.27	0.57	0	3
out_late	Late development stage	524	0.13	0.38	0	2
out_market	Market stage	524	0.22	0.52	0	4
License-ins	Number of inward licensing					
in_total	Total number	524	1.15	1.59	0	9
in_discovery	Drug discovery stage	524	0.32	0.76	0	6
in_early	Early development stage	524	0.38	0.69	0	5
in_late	Late development stage	524	0.15	0.40	0	2
in_market	Market stage	524	0.31	0.67	0	5
Pipeline	Number of drug pipelines					
p_total	Total number	524	28.65	24.24	0	165
p_early	Early development stage	524	5.75	5.71	0	36
p_late	Late development stage	524	4.45	3.83	0	23
p_market	Market stage	524	18.46	16.79	0	119
sales	Real sales in drug businesses (hundred billion yen)	501	1.48	2.12	0.02	15.09
sales_growth	Yearly sales growth	496	0.02	0.18	−1.39	1.66
scope	Firm sales diversity in 16 therapeutic fields	491	3.32	1.51	1.00	7.73
comp_develop	Weighted competition index in the development stages	504	−0.22	2.07	−14.75	3.38
comp_market	Weighted competition index in the product market	491	−0.05	1.36	−7.59	2.51

Note 1: See section 2.2 for the division of licensing and pipeline stages.
Note 2: See section 4.1 and Appendix B for the detailed definition of diversity and competition indexes.

Table 3: Determinants of license-outs of pharmaceutical firms
Dependent variable: *out_total*

	Random effect tobit	Random effect probit	Random effect IV
	out_total	***out_total***	***out_total***
Pipeline			
p_total	0.022*** (0.009)	0.019*** (0.007)	0.012** (0.005)
sales	−0.179* (0.102)	−0.120* (0.073)	−0.101* (0.058)
sales_growth	−0.306 (0.641)	−0.129 (0.485)	−0.357 (0.411)
scope	0.176** (0.089)	0.150** (0.070)	0.079* (0.047)
comp_develop	0.151*** (0.056)	0.078** (0.038)	0.055** (0.025)
comp_market	0.075 (0.097)	0.046 (0.071)	0.036 (0.051)
constant	−2.247*** (0.476)	−1.774*** (0.355)	0.189 (0.211)
d_year	included	included	included
Number of observations	448	448	401
Number of groups	51	51	50
	Log likelihood = -522.867	Log likelihood = -263.165	Instrumented: *p_total* Instruments: one-year lag of *p_total*

Note 1: Level of significance: *** 1%, ** 5%, * 10%.
Note 2: Standard error is given in parenthesis.

Table 4: Determinants of license-outs at four stages of pharmaceutical firms
Dependent variable: *out_discovery*, *out_early*, *out_late*, *out_market*

	Random effect tobit				Random effect probit				Random effect IV			
	out_discovery	***out_early***	***out_late***	***out_market***	***out_discovery***	***out_early***	***out_late***	***out_market***	***out_discovery***	***out_early***	***out_late***	***out_market***
Pipeline												
p_early	0.194**	0.063**	−0.045	−0.008	0.088***	0.038**	−0.029	−0.006	0.017***	0.034***	0.008	−0.002
	(0.076)	(0.026)	(0.038)	(0.029)	(0.029)	(0.018)	(0.024)	(0.021)	(0.004)	(0.013)	(0.007)	(0.013)
p_late	0.362**	−0.024	0.095	−0.064	0.164**	−0.010	0.059	−0.046	0.025***	0.014	0.002	−0.025
	(0.170)	(0.051)	(0.064)	(0.043)	(0.068)	(0.038)	(0.040)	(0.033)	(0.008)	(0.024)	(0.015)	(0.023)
p_market	−0.042	−0.001	0.019	0.043***	−0.016	−0.003	0.014	0.033***	−0.004*	−0.004	0.003	0.009**
	(0.037)	(0.012)	(0.015)	(0.013)	(0.016)	(0.010)	(0.009)	(0.010)	(0.002)	(0.005)	(0.003)	(0.004)
sales	−0.558*	−0.180**	−0.176	0.019	−0.249*	−0.086	−0.113	0.005	−0.036***	−0.060*	−0.028*	0.014
	(0.311)	(0.090)	(0.112)	(0.090)	(0.134)	(0.070)	(0.071)	(0.064)	(0.011)	(0.032)	(0.017)	(0.033)
sales_growth	1.320	−0.250	−1.057	−0.150	0.685	−0.016	−0.481	−0.064	0.086	−0.338	−0.049	0.070
	(1.929)	(0.694)	(1.124)	(0.923)	(0.905)	(0.495)	(0.678)	(0.651)	(0.100)	(0.246)	(0.170)	(0.230)
scope	−0.312	0.221***	0.134	0.078	−0.147	0.178***	0.068	0.078	−0.011	0.062**	0.017	0.025
	(0.296)	(0.082)	(0.099)	(0.083)	(0.131)	(0.064)	(0.065)	(0.067)	(0.008)	(0.027)	(0.016)	(0.026)
comp_develop	−0.013	0.179***	0.286**	−0.109**	−0.007	0.097**	0.189**	−0.080**	0.005	0.034**	0.020**	−0.031**
	(0.128)	(0.065)	(0.133)	(0.055)	(0.062)	(0.045)	(0.085)	(0.040)	(0.005)	(0.015)	(0.010)	(0.014)
comp_market	0.293	0.176*	−0.016	−0.004	0.140	0.116*	−0.012	−0.015	0.008	0.044	0.002	0.004
	(0.316)	(0.093)	(0.098)	(0.042)	(0.152)	(0.070)	(0.066)	(0.033)	(0.008)	(0.027)	(0.016)	(0.012)
constant	−7.166***	−2.393***	−3.594***	−2.929***	−8.928***	−1.826***	−2.154***	−2.002***	0.112**	0.156	0.022	0.268*
	(2.144)	(0.530)	(0.811)	(0.694)	(0.604)	(0.363)	(0.432)	(0.459)	(0.048)	(0.131)	(0.082)	(0.142)
d_year	included	included	included	included	included	included	included	included	included	included	included	included
Number of observations	448	448	448	448	448	448	448	448	401	401	401	401
Number of groups	51	51	51	51	51	51	51	51	50	50	50	50
Log likelihood	-62.375	-326.923	-203.462	-289.179	-52.598	-212.798	-145.828	-190.398	Instrumented: *p_early, p_late, p_market* Instruments: one-year lag of *p_early, p_late, p_market*			

Note 1: Level of significance: *** 1%, ** 5%, * 10%.
Note 2: Standard error is given in parenthesis.

Table 5: Determinants of license-ins of pharmaceutical firms
Dependent variable: *in_total*

	Random effect tobit	Random effect probit	Random effect IV
	in_total	***in_total***	***in_total***
Pipeline			
p_total	−0.011 (0.011)	−0.003 (0.008)	−0.023** (0.010)
sales	0.613*** (0.130)	0.364*** (0.118)	0.644*** (0.102)
sales_growth	0.703 (0.707)	0.275 (0.501)	0.380 (0.572)
scope	0.210** (0.106)	0.139** (0.070)	0.101* (0.058)
comp_develop	−0.089* (0.046)	−0.122** (0.053)	−0.055 (0.034)
comp_market	−0.058 (0.107)	−0.040 (0.070)	0.011 (0.072)
constant	−1.302** (0.502)	−0.875*** (0.315)	0.254 (0.332)
d_year	included	included	included
Number of observations	448	448	401
Number of groups	51	51	50
	Log likelihood = -644.654	Log likelihood = -237.831	Instrumented: *p_total* Instruments: one-year lag of *p_total*

Note 1: Level of significance: *** 1%, ** 5%, * 10%.
Note 2: Standard error is given in parenthesis.

Table 6: Determinants of license-ins at four stages of pharmaceutical firms
Dependent variable: *in_discovery*, *in_early*, *in_late*, *in_market*

	Random effect tobit				Random effect probit				Random effect IV			
	in_discovery	***in_early***	***in_late***	***in_market***	***in_discovery***	***in_early***	***in_late***	***in_market***	***in_discovery***	***in_early***	***in_late***	***in_market***
Pipeline												
p_early	−0.005 (0.028)	0.004 (0.024)	−0.012 (0.028)	0.053** (0.027)	−0.016 (0.022)	−0.014 (0.019)	−0.007 (0.021)	0.025 (0.019)	−0.02 (0.015)	0.008 (0.015)	−0.006 (0.009)	0.056*** (0.016)
p_late	0.062 (0.053)	0.009 (0.044)	−0.026 (0.050)	−0.037 (0.050)	0.024 (0.043)	−0.003 (0.033)	−0.034 (0.039)	−0.022 (0.029)	0.040 (0.027)	−0.023 (0.026)	−0.018* (0.009)	−0.074** (0.030)
p_market	−0.029** (0.014)	−0.023** (0.011)	−0.017 (0.012)	0.001 (0.013)	−0.018 (0.012)	−0.015* (0.008)	−0.009 (0.009)	0.006 (0.010)	−0.013** (0.005)	−0.011** (0.005)	−0.004 (0.003)	−0.004 (0.005)
sales	0.555*** (0.112)	0.392*** (0.092)	0.376*** (0.109)	0.105 (0.091)	0.430*** (0.106)	0.301*** (0.079)	0.280*** (0.080)	0.041 (0.068)	0.261*** (0.049)	0.199*** (0.048)	0.128*** (0.028)	0.110** (0.044)
sales_growth	−0.129 (0.807)	0.935 (0.684)	0.641 (0.884)	−0.413 (0.873)	0.031 (0.550)	0.577 (0.483)	0.442 (0.602)	−0.354 (0.605)	−0.178 (0.295)	0.339 (0.307)	0.138 (0.174)	0.192 (0.293)
scope	0.127 (0.097)	−0.043 (0.072)	0.051 (0.086)	0.234*** (0.086)	0.086 (0.082)	−0.014 (0.055)	0.032 (0.060)	0.170*** (0.062)	0.002 (0.028)	−0.003 (0.028)	0.002 (0.016)	0.060* (0.031)
comp_develop	0.053 (0.058)	−0.013 (0.043)	0.023 (0.056)	−0.135*** (0.044)	0.015 (0.045)	−0.003 (0.031)	0.019 (0.040)	−0.083** (0.034)	0.012 (0.016)	0.006 (0.017)	0.003 (0.010)	−0.059*** (0.018)
comp_market	−0.004 (0.082)	−0.094 (0.063)	0.203** (0.101)	−0.029 (0.082)	−0.001 (0.073)	−0.057 (0.051)	0.128* (0.069)	−0.064 (0.063)	0.013 (0.029)	−0.034 (0.028)	0.039** (0.016)	0.007 (0.031)
constant	−2.606*** (0.589)	−1.594*** (0.458)	−3.002** (0.729)	−2.785*** (0.553)	−1.803*** (0.415)	−1.037*** (0.305)	−2.040*** (0.449)	−1.843*** (0.362)	−0.098 (0.150)	0.316** (0.151)	0.080 (0.085)	−0.024 (0.150)
d_year	included	included	included	included	included	included	included	included	included	included	included	included
Number of observations	448	448	448	448	448	448	448	448	401	401	401	401
Number of groups	51	51	51	51	51	51	51	51	50	50	50	50
Log likelihood	-315.122	-399.139	-211.729	-349.259	-173.189	-243.026	-148.128	-219.383	Instrumented: *p_early, p_late, p_market* Instruments: one-year lag of *p_early, p_late, p_market*			

Note 1: Level of significance: *** 1%, ** 5%, * 10%.
Note 2: Standard error is given in parenthesis.