International Journal of Humanities and Social Science Invention
ISSN (Online): 2319 – 7722, ISSN (Print): 2319 – 7714
www.ijhssi.org ||Volume 5 Issue 8||August. 2016 || PP.25-33

Determinants of New Molecular Entity Approval by United States Food & Drug Administration (2006-2015)

Karina Eka Putri[1, 2], Raymond R. Tjandrawinata[1, 2 *], Yanti[2]
[1]*Dexa Laboratories of Biomolecular Sciences (DLBS), PT Dexa Medica, Indonesia*
[2]*Faculty of Biotechnology, Atma Jaya Catholic University, Indonesia*

ABSTRACT: *This paper analyzes the relationship between research-based pharmaceutical companies' R&D productivity, patent, pivotal trial and drug development strategy with the number of NME approval by U.S. FDA. The model was estimated using annual data, gathered from ten large pharmaceutical companies in the world. The regression analysis used pooled regression with Estimated Generalized Least Squares (EGLS) method. The result showed that R&D productivity, patent, pivotal trial, and drug development strategy are statistically significant in increasing the number of NME approval in research-based pharmaceutical companies. The relative order of significance in influencing the number of NME approval was patent, development strategy, R&D productivity, and pivotal trial.*

Keywords: *Development Strategy, FDA Approval, New Molecular Entity, Patent, Pivotal Trial, R&D productivity*

I. Introduction

Pharmaceutical research and development (R&D) that leads to the discovery of new drugs have led to reduced side effects and hospitalizations, improvement in health, quality of life and increased life expectancy of patients [1]. Drug discovery and development is a long and systematic process which requires resilient commitment and collaboration of interdisciplinary knowledge from various scientific domains [2]. For every 5,000 to 10,000 experimental compounds considered, typically one will gain market approval, after an average of more than 10 years of research and development costing an average of $2.6 billion [1].

Despite the huge efforts had done by the pharmaceutical companies in the creation of new medicine, the critical decision for market approval is outside the control of the companies [2]. In the United States, new drug market approval rests with the Food and Drug Administration (FDA), the government agency that is responsible in assuring the safety and efficacy of the drug marketed. The FDA reviews the pharmaceutical companies' application to market the drug in the United States and issues the market approval.

The new-drug discovery and development process consists of four stages: basic research, drug discovery, preclinical trials and clinical trials, as shown in Fig. 1. Basic research is conducted to understand the disease or the condition, to identify and validate the target molecule and to determine the field of compounds that may interact with the target molecule. In drug discovery, researchers narrow down the field of compounds to lead compounds – promising molecules that could influence the target and, potentially, become a medicine. The researchers preliminary assess the safety of the lead compounds by studying its pharmacokinetics. Lead compound(s) which pass the initial screening are then optimized or altered to make them more effective and safer. These modified lead compound(s) are subjected to preclinical tests where researchers determine whether the drug(s) is safe for human testing.

After conducted preclinical tests, pharmaceutical company submit Investigational New Drug (IND) application to regulatory agency, Food and Drug Administration (FDA). In the application, the company must include animal study data and toxicity data, manufacturing information, clinical protocols for trials to be conducted, data from any prior human research and information related to the investigator. The IND submissions are expected to protect volunteers who participate in clinical trials from unreasonable and significant risk in clinical trials [3]. Upon approval of the IND, the company can start the clinical trials.

Clinical trials of the new drug are typically conducted in three phases. In phase 1 trials, the candidate drug is tested in human for the first time. These studies are usually conducted with a small number of healthy volunteers. The main goal is to assess the safety of the drug when used in humans. The safe dosing range is also determined in these trials. In phase 2 trials, the researchers evaluate the candidate drug's effectiveness in hundreds of patient volunteers with the disease or condition under study. In these trials, researchers also analyze the optimal dose strength, drug regimen, and examine possible short-term side effects. Phase 3 trials generate statistically significant data related to the safety, efficacy and the overall benefit-risk relationship of the investigational drug. These trials may enroll thousands of patient volunteers. Phase 3 trials are both the costliest and longest trials. After completed the clinical trials, the company submit a New Drug Application (NDA) to the FDA.

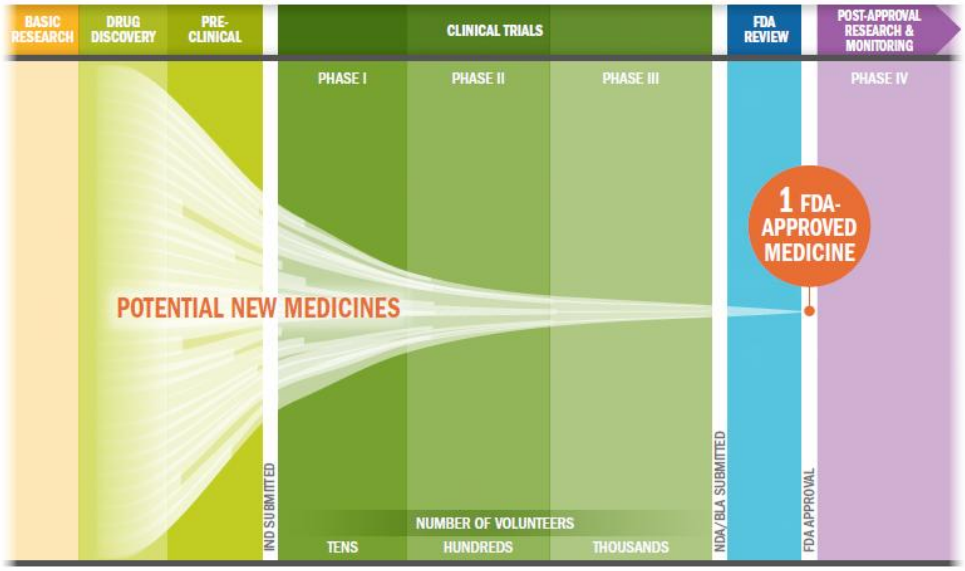

Figure 1: New-drug discovery and development process [1]. IND: Investigational New Drug; NDA: New Drug Application; BLA: Biologic License Application; FDA: Food and Drug Administration.

Along with the trial results, the company must include product information (including raw material, composition, manufacturing and packaging processes as well as production facility), proposed labeling, safety update, drug abuse information, patent information, data from studies conducted outside the U.S., institutional review board compliance information, and directions for use in the NDA. The FDA has 6 until 10 months to make a decision on whether to approve the NDA. During the review, the FDA has to establish that the drug is safe and effective in its proposed use. The complete reports from "adequate and well-controlled investigations" are the primary basis for FDA in determining whether there is substantial evidence to support the claims of effectiveness for new drugs [4]. These "adequate and well-controlled investigations" are identified as the Pivotal Trials.

Although there are ten types of NDA based on characteristics of the product in the application, for the purpose of this research, only type 1 NDA was used. A type 1 NDA is for a drug product that contains a new molecular entity (NME). An NME is an active ingredient that contains no active moiety that has been previously approved or has been previously marketed as a drug in the United States [5]. Previous data showed that both pharmaceutical company and the FDA played vital roles in promoting the new-drug approvals [6]. Specifically, it is stated that an increase in the number of filings of NME by pharmaceutical companies and a decrease in average FDA review times drove the surge of new-drug approvals.

Through this research, we examine four factors in the pharmaceutical companies that are assumed to be the determinants in the number of approvals from U.S. FDA. These factors are R&D productivity, patent, pivotal trial and development strategy. The aim of this study is to determine the relationship between pharmaceutical companies' R&D productivity, patents, pivotal trials and development strategies with the number of NME approval, for the period of 2006 until 2015.

II. Data Collection And Methodology

Samples used in this study consists of ten large pharmaceutical companies i.e. Novartis, Pfizer, F. Hoffman La-Roche, Sanofi Aventis, Merck & Co., Johnson & Johnson, GlaxoSmithKline, AstraZeneca, Gilead Sciences and Takeda Pharmaceuticals. The NME approval data every year were obtained from FDA database. Annual financial reports of each company from 2001 until 2015 were used to obtain the number of R&D expenditure. Patent data for each approved drug were retrieved from Orange Book U.S. FDA. Pivotal trial data for each approved drug were obtained from Medical Review records in U.S. FDA database. Data on the development strategies is retrieved from the public online sources.

This study was conducted by pooled regression analysis using Estimated Generalized Least Squares (EGLS) method with constant-coefficients model or random effect model. The EGLS method was applied to correct heteroscedasticity and/or autocorrelation [7]. In constant-coefficients model (or pooled estimators model), the slope coefficients are constant across subjects and the error term is uncorrelated with the regressors [7, 8]. In random effect model, each cross-section intercept has random deviation to the common intercept's mean value [7]. The regression analysis was done using econometric software, Eviews® 9.5 Student Version (IHS Inc., United States of America).

The number of NME approval each year for each company served as dependent variable in the regression analysis (hereafter referred to as 'APPROVAL'). Independent variables, which were representing each factor, were selected. R&D expenditure five years before approval (hereafter referred to as 'RNDE (-5)') was used as the proxy for R&D productivity. The unit for RNDE (-5) was billion U.S. dollar. The number of granted patents at the time of NDA submission (hereafter referred to as 'GRANTED') was used as the proxy for patent. Four key features of the Pivotal Trial i.e. the number of pivotal trials identified by the FDA (hereafter referred to as 'PIVOTAL'), the number of randomized and double-blinded pivotal trials (hereafter referred to as 'DESIGN'), the number of pivotal trials using clinical outcome as primary endpoint (hereafter referred to as 'CLINICAL'), and the number of pivotal trials using surrogate endpoint as the primary endpoint (hereafter referred to as 'SURROGATE') were used as the proxy for pivotal trial. Meanwhile, the number of drugs developed on company's own (hereafter referred to as 'OD'), the number of drugs developed through merger & acquisition (hereafter referred to as 'MNA'), the number of drugs developed through licensing (hereafter referred to as 'LC'), the number of drugs developed through strategic partnership (hereafter referred to as 'SP'), and the number of drugs developed through collaborative development (hereafter referred to as 'CD') were used as the proxy for development strategy.

The following principal hypotheses were tested: (1) five-year lagged RNDE would have positive relationship with the APPROVAL; (2) an increase in the GRANTED would increase the APPROVAL; (3) an increase in the PIVOTAL would increase the APPROVAL; (4) an increase in the DESIGN would increase the APPROVAL; (5) CLINICAL would have positive relationship with the APPROVAL; (6) SURROGATE would have positive relationship with the APPROVAL; (7) an increase in the OD would increase the APPROVAL; (8) an increase in the MNA would increase the APPROVAL; (9) an increase in the LC would increase the APPROVAL; (10) an increase in the SP would increase the APPROVAL; an (11) an increase in the CD would increase the APPROVAL.

III. Results AND DISCUSSION

Through the estimation using pooled regression model, the values of the coefficient estimates were obtained. Regression analysis results for each factor depicted in Table I. As can be seen in Table I, there were positive and significant correlations between the RNDE (-5), GRANTED, PIVOTAL, CLINICAL, OD, MNA, LC, SP, and CD with the APPROVAL. While negative correlations occurred between the DESIGN and SURROGATE with the APPROVAL. To determine the order of significance between each factor, regression analysis was done using most significant independent variables which were selected from each factor. The results were shown in Table II.

3.1. R&D Productivity

As shown in Table I, the coefficient of determination (R^2 or R-squared) for RNDE (-5) was 0.084. It means only 8.4% variation in the number of NME approvals that can be explained by the variation of R&D expenditure 5 years before the approval; the rest 91.6 % variation can be explained by the variation of independent variables outside the R&D model. It also means that the R&D model did not fit well with the data. However, according to the t-Statistic and probability value, the variation in the RNDE (-5) was significant in predicting the variation of NME approval.

In the research-based pharmaceutical firms, R&D process spans from the early discovery process until the end of clinical trials. The average cost to research and develop each successful drug is estimated to be $2.6 billion [9]. Since the cost to develop a medicine in pharmaceutical company is very high, R&D spending every year has grown faster, because at present many companies choose to invest their money in research and development in order to gain future revenues [10]. Previous study found that R&D spending in the previous year is positively and significantly affect the sales revenue in multinational pharmaceutical companies [11].

Although investment in pharmaceutical R&D has increased substantially in this time, the lack of a corresponding increase in the output in terms of new drugs being approved during six years (2005-2010) indicates that therapeutic innovation has become more challenging [12, 13]. This phenomenon were believed due to increasing concentration of R&D investment in more complex diseases and higher risk of failure which correspond to unmet therapeutic needs and unexploited biological mechanisms, increasing regulatory requirement in clinical trials results, greater focus on targeting chronic and degenerative disease [1, 12].

However, the number of NMEs is an imperfect measure of R&D outcomes, as it does not reflect changes in the quality of the output [12]. In addition, the productivity crisis might be a temporary phenomenon, as radical technological changes, which could initially increase the time lag between investment and outcome, thereby reducing R&D productivity in the short term [14]. Therefore, the impact of R&D investment to the number of approval might not be apparent at a certain time. It should be noted that the investment for one particular drug would be dispersed throughout the discovery and development years.

On average, it takes at least ten years for a new medicine to complete the journey from initial discovery to the marketplace, with clinical trials alone taking six to seven years on average [1]. Since clinical trial is the most expensive process in the drug development, the peak R&D investment for one particular drug probably occurs 5-6 years before the approval. The regression results showed that enhancement in R&D expenditure 5 years before approval is significantly associated with the increase in the number of FDA approvals at the current year.

3.2. Patent

The regression results for GRANTED showed the coefficient of determination was 0.70 which means that 70% variation in the APPROVAL were associated with the variation in the GRANTED. Based on the t-Statistic and probability value, the variable of GRANTED was significant in predicting the number of NME approvals by U.S. FDA. An increase of 1 granted patent will be accompanied with an increase of 0.21 in the number of approvals. The results supported the hypothesis that granted patent would have positive relationship with the number of approvals.

Drug discovery and development process contains information-rich knowledge that constitutes intellectual property of the company. Once the information is publicly available, it became a simple technical matter for a competitor to duplicate. Therefore patents play a vital role in encouraging the research & development of new drugs and are essential for the investments in R&D [15]. As also stated by Baker [16], patents are tools to incentivize future investments in R&D and maximize the profitability in pharmaceutical industry. The significant role of patents in pharmaceuticals has emerged in various studies. For example, in a study by Levin et al. [17] of 130 separate lines of business, pharmaceuticals ranked among the top few in terms of the importance of patents for appropriating R&D returns. Patents are considered essential by start-up biotech firms for securing the funding for the expensive and time-consuming clinical testing required to gain FDA approval [18].

In the U.S., patents can be filed to the Patent and Trademark Office (PTO) since the early stages of drug development and might be granted anytime along the development lifeline of a drug. For pharmaceutical patent, the period between the approval of the drug and expiration of the patent is called Effective Patent Life where the company can recoup the great costs incurred during drug discovery and development optimally. Since patent only lasts for 20 years from the filing date, the effective patent life can be lost because of the lengthy periods required for clinical trials and regulatory approval [15]. Accordingly, the faster the drug is approved and enters the market, the longer the marketing period and thus the generation of revenues and profits. Fernandez et al. [19] in their article stated that FDA approval is accelerated for patented compounds. This implies that FDA review times are shorter for patented compounds, thus patents are indirectly increasing the number of approved drugs. The statement is consistent with the results as shown in Table I in which the increase in the number of granted patents at the time of NDA submission to FDA would likely increase the number of FDA approvals.

3.3. Pivotal Trial

The regression results for pivotal trial showed that changes in all the independent variables were significantly associated with the changes the number of approval, except for SURROGATE. The coefficient of determination value was 0.74, which means that 74% variation in the number of approvals can be explained by the variation in the number of PIVOTAL, DESIGN, CLINICAL, and SURROGATE. The F-statistic showed that overall estimation was statistically significant. An increase of 1 unit in the number of pivotal trial and the number of pivotal trial using clinical endpoint as the primary endpoint will be accompanied by an increase of 0.51 and 0.31, respectively, in the number of approvals. Meanwhile, an increase of 1 randomized & double-blinded pivotal trial will be accompanied by a decrease of 0.27 in the number of approvals. The result showed that PIVOTAL is the most significant variable in estimating the FDA approvals.

Pivotal trials are usually Phase 3 trials aiming to prove a drug's effectiveness and safety (the benefits of the drug outweigh the risks) [20]. The FDA guidance suggests that, to establish effectiveness of a new drug in NDA submission, pharmaceutical company have to submit at least two pivotal trials in which independent evidence of efficacy is provided by each of them [21]. A single clinical experimental finding of efficacy, unsupported by other independent evidence, has not usually been considered adequate scientific support for a conclusion of effectiveness [21]. The regression results were in accordance with the FDA guidance and the hypothesis. More pivotal trial most likely will be correlated with more clinical evidence of efficacy, thus increasing the probability of approval and eventually number of approval.

With respect to the trial design, the FDA regulations stated that the pivotal trial must use a design that permits a valid comparison with a control to provide a quantitative assessment of drug effect [4]. To conform to the regulation, the trial usually designed as randomized and double-blinded trial. The advantages of a rigorous, randomized, well-controlled clinical trial is that it can establish causation, limit the placebo effect, avoid spurious conclusions, and yield reliable information [21]. Thus, theoretically, there should be positive

relationship between the number of randomized and double-blinded pivotal trial and the number of FDA approvals. However, the regression results showed that the relationship was negative.

The FDA approvals can be made without requiring costly and time-consuming randomized and double-blinded trials, despite their being regarded as the gold standard for evaluation [22, 23]. Randomization of pivotal trial is usually preferable but not always possible for the following reasons: ethical consideration, patient availability, and very small studies [20]. The FDA allows for a customized approach to approval, including the ability to rapidly approve potentially effective therapies for life-threatening diseases, such as certain cancers, or those diseases for which there is no existing effective treatment, such as orphan diseases [24].

Primary endpoint is the main measurement that determines whether the treatment has worked [20]. It must meet 3 criteria: clinically relevant, sensitive to treatment effect, measurable and interpretable [25]. Clinical trial endpoints in the Phase 3 trials commonly evaluate whether a drug provides a clinical benefits to the patients. Clinical benefits for supporting drug approval have included important clinical endpoint but have also included effects on established surrogate endpoints [26].

A clinical endpoint is a characteristic or variable that reflects how a patient feels or functions or how long a patient survives [25]. The regression result showed that there were statistically significant and positive relationship between the number of pivotal trial using clinical endpoint as the primary endpoint and the number of FDA approvals. Typically, drugs are approved on the basis of adequate and well-controlled clinical trials that permit the conclusion that the drug has a beneficial effect on a clinical outcome that is directly and obviously related to the patient's clinical status [27]. The regression results are in line with the hypothesis and the theory.

A surrogate endpoint is a biomarker that is intended to substitute for a clinical endpoint, i.e., a biomarker that is expected to predict clinical benefit [25]. Surrogate endpoints are used if clinical endpoints are not practical or feasible, too costly or causing too much discomfort to patient to be measured. However, surrogate endpoint is never as informative as the clinical endpoint, and in many examples, surrogate endpoints have turned out not to be predictive of clinical response at all [20]. Therefore, the increase in the number of pivotal trials using surrogate endpoint as the primary endpoint cannot increase the number of FDA approvals, as shown in Table I.

3.4. Development Strategy

Development strategy regression results as shown in Table I indicated that each strategy, own development, merger & acquisition, license, strategic partnership or collaborative development, was statistically significant in increasing the number of FDA approvals. The coefficient of determination was 0.43 for OD, 0.26 for MNA, 0.23 for LC, 0.34 for SP, and 0.77 for CD. An increase in the number of drugs developed by company's own will be accompanied by an increase of 0.98 in the number of approvals. An addition of one drug developed through merger and acquisition will be accompanied by an increase of 1.13 in the number of approvals. An increase in the number of drug developed through license will be accompanied with an increase of 1.14 in the number of approvals. An increase in the number of drug developed through strategic partnership will be accompanied with the increase of 1.16 in the number of approvals. An increase in the number of drug developed through collaborative development will be accompanied by an increase of 1.04 in the number of approvals. The estimation models showed that the drug developed through collaborative development is most significant in predicting the FDA approvals.

The most ideal and practical way in research-based companies to increase the number of FDA approvals is to increase own R&D productivity in drug discovery and development. Private pharmaceutical companies recognize the importance of investing in their own R&D so that they can build and maintain the skills, the knowledge, and the organizational routines to identify and utilize the research output of others [28]. Companies that underestimate the importance of conducting internal R&D would not only curtail their own capability to originate novel drugs but may also relinquish their ability to benefit from the innovations of others [2]. Regression results showed that the increase in the number of drugs developed by company's own significantly increase the number of FDA approvals. Increasing own R&D productivity would likely result in the increase of the number of potential new drugs.

Pharmaceutical companies frequently collaborate with other parties such as academic research institute, clinical research organization, government laboratory, hospital and other pharmaceutical company in drug discovery and development. A multi-tier system of organizations supplementing each other's competencies might be best equipped to handle the complexities of modern drug innovation both efficiently and effectively [2]. There are multiple types of interfirm collaboration that are used by pharmaceutical companies. It depends on the risks, usually associated with exclusivity rights, unpredictable outcomes, competition, and first-to-market races [2]. Generally, it is the companies experiencing a decline in new drug productivity (measured as depletion in their research pipeline) that are more likely to engage in R&D-focused alliances, in-licensing agreements, or consolidation through mergers and acquisitions [29]. The collaboration can invigorate companies' internal research efforts and extend their research pipelines [30]. The regression results as shown in Table I indicated

that collaborative development is positively and significantly affecting the number of FDA approvals. The result was consistent with the theory and hypothesis.

Pharmaceutical companies have often engaged in merger and acquisition activity to address the erratic nature of the drug discovery process [31]. The motives for merger and acquisitions activity can be broadly categorized into adaptive and proactive [32]. Two studies found that pipeline gaps and issues continue to be a key adaptive driver of merger activity [29, 33]. Proactive motives for mergers include increases in size to achieve critical mass and economies of scale in R&D, to increase the number of therapeutic areas in their R&D programs to take advantage of economies of scope, to bring new technologies and research tools into the firm to enhance their research productivity, as well as to increase firm size and growth rates [32].

Previous study by CenterWatch indicated a reduction in development projects after the merger was implemented [34]. As long as these reductions in R&D activities eliminated duplicate efforts or projects with low probability of success, or facilitated more external alliances, the companies' R&D performance could have increased in the post-merger period compared to the pre-merger one [32]. Previous research stated that following merger & acquisition activities, the increases in the sales revenue and R&D intensity are significantly associated with the increase in the number of NME approval in research-based pharmaceutical company [35]. Apparently the increase in the number of drug approval also occurred in generic pharmaceutical companies post mergers & acquisitions through the increase in the R&D expenditure, profitability and R&D intensity [36]. The regression results are consistent with the theory. Increase in the number of drug developed through merger & acquisition would be associated with the increase in the number of FDA approvals.

For large pharmaceutical companies, in-licensing is a shortcut to fill their product pipelines and extend their research portfolios. As continuous innovation is imperative in the pharmaceutical industry, replenishing drug pipelines on a regular basis is crucial for maintaining a strong competitive standing [2]. In-licensing is a rather desirable business strategy geared for the realization of synergies, reduction in effort duplication, and ultimately, more efficient use of firms' resources. The benefits of adopting an in-licensing approach is that it allows large pharmaceutical companies to spend less money to selectively choose the most beneficial compounds that they desire instead of having to acquire the whole organization dealing with the added complication of merging the two organizations [31]. Therefore in-licensing can increase the R&D productivity in pharmaceutical companies and increase the probability of gaining FDA approval. The results were consistent with the theory; an increase in the number of drugs developed through in-licensing will be accompanied with the increase in the number of FDA approvals.

Strategic partnerships or alliances represent a symbiotic collaboration between the small biotech and the large pharmaceutical firms. Rothaermel found that large pharmaceutical firms prefer exploitation alliances (that leverage their downstream assets: clinical trials, FDA regulatory management, marketing, sales) than exploration alliances (that build their upstream, technology-based competencies: drug discovery and development) [37]. Exploitation alliances can leverage the already existing specialized downstream assets of large pharmaceutical firms, help them capture significant amounts of revenue, as well as sustain their reputation as innovators while limiting the amount of extra risk involved [2]. Additionally, products developed in an alliance tend to have a higher probability of success, at least for the more complex phase 2 and phase 3 trials, particularly if the licensee is a large firm [38]. Increasing probability of success means higher probability of gaining FDA approval. Therefore, increase in the number of drugs developed through strategic partnerships or alliances will be accompanied by the increase in the number of FDA approvals.

Table I: Regression results for all variables

Dependent Variable: APPROVAL					
Total panel observations: 100					
Method: Pooled EGLS (Cross-section weights)					
Independent Variable	**Coefficient**	**t-Statistic**	**Prob.**	**R^2**	**F-Statistic**
C	0.358657	2.529798**	0.0130	0.084107	8.999434***
RNDE(-5)	0.083386	2.999906***	0.0034		
Method: Pooled EGLS (Cross-section random effects)					
Independent Variable	**Coefficient**	**t-Statistic**	**Prob.**	**R^2**	**F-Statistic**
C	0.329656	3.448903***	0.0008	0.702176	231.0535***
GRANTED	0.211522	15.17313***	0.0000		
Method: Pooled EGLS (Cross-section weights)					
Independent Variable	**Coefficient**	**t-Statistic**	**Prob.**	**R^2**	**F-Statistic**
C	0.229628	4.290006***	0.0000	0.742851	68.609***
PIVOTAL	0.513419	5.891265***	0.0000		
DESIGN	-0.271818	-4.474057***	0.0000		
CLINICAL	0.213599	2.681672***	0.0086		
SURROGATE	-0.065653	-0.951787	0.3436		

Method: Pooled EGLS (Cross-section weights)					
Independent Variable	**Coefficient**	**t-Statistic**	**Prob.**	**R^2**	**F-Statistic**
C	0.507741	6.900623***	0.0000	0.42851	73.48159***
OD	0.985937	8.57214***	0.0000		
Method: Pooled EGLS (Cross-section weights)					
Independent Variable	**Coefficient**	**t-Statistic**	**Prob.**	**R^2**	**F-Statistic**
C	0.525084	6.474493***	0.0000	0.258003	34.07599***
MNA	1.12869	5.837464***	0.0000		
Method: Pooled EGLS (Cross-section weights)					
Independent Variable	**Coefficient**	**t-Statistic**	**Prob.**	**R^2**	**F-Statistic**
C	0.551465	6.675938***	0.0000	0.232507	29.68841***
LC	1.143383	5.448707***	0.0000		
Method: Pooled EGLS (Cross-section weights)					
Independent Variable	**Coefficient**	**t-Statistic**	**Prob.**	**R^2**	**F-Statistic**
C	0.495735	6.294115***	0.0000	0.341643	50.85531***
SP	1.162787	7.131291***	0.0000		
Method: Pooled EGLS (Cross-section weights)					
Independent Variable	**Coefficient**	**t-Statistic**	**Prob.**	**R^2**	**F-Statistic**
C	0.143600	2.725619***	0.0076	0.765817	320.4757***
CD	1.044126	17.90183***	0.0000		

Two-tail significance levels: ** Significant at level 5 %; *** Significant at level 1 %. EGLS: Estimated Generalized Least Squares. C: constant. Prob.: t-Statistic probability. R^2: coefficient of determination.

3.5. The Significance of All Factors

Regression results for all determinant factors showed that all factors, R&D productivity as represented by the amount of R&D expenditure 5 years before approval, patent as represented by the number of granted patent at the time of NDA submission, pivotal trial as represented by the number of pivotal trials, and development strategy as represented by the number of drugs developed through collaborative development, were statistically significant in estimating the number of NME approvals by United States FDA as shown in Table II. Coefficient of determination at 0.8389 indicated that 83.89% variation in the number of approvals can be explained by the variation in the RNDE(-5), GRANTED, PIVOTAL, and CD.

Negative constant value showed that the absence of all these factors lead to negative NME approval. However, as can be seen in Table II, the t-statistic showed that constant value is insignificant which is suggesting that there are other factor(s) outside the model that might affect the number of NME approval. Based on the comparison of t-statistic of each selected variable from each factor, the order of significance was obtained. Granted patent was the most significant variables, followed by collaborative development, R&D expenditure 5 years before approval, and pivotal trial.

The regression results from Table II suggested that patent is the most significant factor that affecting the number of NME approvals. Although there seems to be no direct causality between granted patents and FDA approvals, patent were considered as the most important and necessary factor in appropriating the benefits from innovations. It should be noted that imitation costs in pharmaceuticals are extremely low relative to the innovator's costs for discovering and developing a new compound [39]. Strong patent protection supports companies' expectations of being able to set prices for new drugs above competitive levels and thus recoup their R&D investment which are crucial to their decisions to innovate [40].

The strategy used by the pharmaceutical company to discover and develop the drug is the second significant factor in predicting the FDA approvals. Discovery and development programs initiated within more rich and diverse investigation portfolios can enhance the efficiency of the innovation process and increase the likelihood of getting FDA approval [2]. Enhancement in the company's portfolios is the result of increasing R&D productivity through internal R&D development and collaboration with other companies. Our data showed that most of the approved NMEs were developed through collaborative development. The collaboration takes form in the merger & acquisition, licensing, and strategic partnership. The collaboration would enrich the company portfolios and increase the probability of gaining FDA approval.

R&D productivity is found to be the third significant factor that affecting the FDA approvals. Since our research used R&D expenditure 5 years before approval as the representation for R&D productivity at the current year, the increase in the R&D expenditure 5 years before approval would be influenced by the decision in the early development. Therefore, R&D expenditure is less significant than the development strategy chosen by the company. The increase in R&D expenditure 5 years before approval is assumed to be correlates with the

increase in investment needed for clinical trial. Therefore, R&D expenditure 5 years before approval is more important factor than pivotal trial.

The regression results from Table II indicated that pivotal trial is the least significant factor which affecting the number of NME approvals. The importance of clinical trial as viewed from both sides; the FDA determines the safety and effectiveness of new drugs from the results of pivotal trials and the pharmaceutical companies allocate most of R&D investment in clinical trial. Successful clinical trials, especially in late phase trials, correspond to higher probability of gaining FDA approval [9]. However, it is an important fact that successful clinical trials are prepared since early development stage. Therefore, the development strategy is still more important factor than the pivotal trial.

Table II: Regression results for selected variables from each factor

Dependent Variable: APPROVAL					
Total panel observations: 100					
Method: Pooled EGLS (Cross-section weights)					
Independent Variable	**Coefficient**	**t-Statistic**	**Prob.**	**R^2**	**F-Statistic**
C	-0.070897	-0.973435	0.3328	0.838926	123.6979***
RNDE(-5)	0.053117	3.876422***	0.0002		
GRANTED	0.095102	6.159108***	0.0000		
PIVOTAL	0.071851	3.534004***	0.0006		
CD	0.427828	5.007143***	0.0000		

Two-tail significance levels: ** Significant at level 5 %; *** Significant at level 1 %. EGLS: Estimated Generalized Least Squares. C: constant. Prob.: t-Statistic probability. R^2: coefficient of determination.

IV. Conclusion

There were statistically significant positive relationships between pharmaceutical companies' R&D productivity, patent, pivotal trial, and development strategy with the number of NME approvals from United States FDA. The relative order of significance of the factors to the number of FDA approvals was patent, development strategy, R&D productivity, and pivotal trial. Although there are reasonable expectations that the relationships would be positive and significant, no previous studies that have combine these four factors as well as compare the significance of each factor to the number of approvals.

Acknowledgements

This work was fully supported by Dexa Medica, Inc. All the information was publicly available at the relevant websites.

References

[1] Pharmaceutical Research and Manufacturers of America, Biopharmaceutical Research Industry Profile, Washington, DC: PhRMA; April 2015.

[2] Petrova, E., Innovation in the Pharmaceutical Industry: The Process of Drug Discovery and Development, in M. Ding, J. Eliashberg, & S. Stremersch (Eds.), *Innovation and Marketing in the Pharmaceutical Industry* (New York: Springer, 2014) Vol. 20, 19–81.

[3] The Drug Development Process, Retrieved from: http://www.fda.gov/ForPatients/Approvals/Drugs/default.htm. Accessed from 1 June to 25 June 2016.

[4] FDA Code of Federal Regulations, Title 21 Sec. 314.126, Retrieved from: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=314.126. Accessed from 1 June to 25 June 2016.

[5] FDA Center for Drug Evaluation and Research, Manual of Policies and Procedures, NDA Classification Code, 2015.

[6] Ma, P., Singh, N., & Smith, J., What's Driving the Surge in New-Drug Approvals. McKinsey & Company, 2013, Retrieved from: http://www.mckinsey.com/industries/public-sector/our-insights/whats-driving-the-surge-in-new-drug-approvals. Accessed 10 June 2016.

[7] Gujarati, D.N. & Porter, D.C., *Basic Econometrics* (5th ed.) (New York: McGraw-Hill/Irwin, 2009).

[8] Cameron, A.C. & Trivedi, P.K., *Microeconometrics: Methods & Applications* (New York: Cambridge University Press, 2005).

[9] DiMasi, J. A., Cost of developing a new drug, Tufts Center for the Study of Drug Development (CSDD), R&D Cost Study Briefing; November 18, 2014, Boston Mass.: CSDD, 2014.

[10] Simanjuntak, D.G. and Tjandrawinata, R.R., Impact of Profitability, R&D Intensity, and Cash Flow on R&D Expenditure in Pharmaceutical Companies, Department of Business Development, Dexa Medica Group, Jakarta, Indonesia, 2011. Retrieved from SSRN: http://ssrn.com/abstract=1824267.

[11] Simanjuntak, D.G and Tjandrawinata, R.R., Factors Influencing Sales Revenue in the Multinational Pharmaceutical Companies, Department of Business Development, Dexa Medica Group, Tangerang, Indonesia, 2011. Retrieved from SSRN: http://ssrn.com/abstract=1898071.

[12] Pammolli, F., Magazzini, L., & Riccaboni, M., The productivity crisis in pharmaceutical R&D, *Nature Reviews. Drug Discovery*, *10(6)*, 2011, 428–438.

[13] Khanna, I., Drug discovery in pharmaceutical industry: productivity challenges and trends, *Drug Discovery Today*, *17(19-20)*, 2012, 1088–1102.

[14] Helpman, E. & Trajtenberg, M., in Helpman, E. (Ed.), *General Purpose Technologies and Economic Growth* (ed. Helpman, E.) (Cambridge: The MIT Press, 1998) 85–119.

[15] Grabowski, H. G., & Vernon, J. M., Effective patent life in pharmaceuticals, *International Journal of Technology Management*, *19(1/2)*, 2000, 98.

[16] Baker, B. K., Ending drug registration apartheid: taming data exclusivity and patent/registration linkage, *American Journal of Law & Medicine, 34(2-3)*, 2008, 303–344.

[17] Levin, R. D., *et al.*, Appropriating the Returns from Industrial Research and Development, *Brookings Papers on Economic Activity. 3*, 1987, 783-820.

[18] Grabowski, H. G. & Vernon, J. M., *The Search for New Vaccines: The Effects of the Vaccines for Children Program* (Washington, D.C.: The American Enterprise Institute Press, 1997).

[19] Fernandez, D.S., Huie, J. and Hsu, J., The Interface of Patents with the Regulatory Drug Approval Process and How Resulting Interplay Can Affect Market Entry, in A. Krattiger, R. T. Mahoney, L. Nelsen, et al. (Eds.), *Intellectual Property Management in Health and Agricultural Innovation: A Handbook of Best Practice*, (Oxford, U. K.: MIHR and Davis, U.S.A.: PIPRA, 2007) Available online at www.ipHandbook.org.

[20] Chin, B. & Lee, B. Y., *Principles and Practice of Clinical Trial Medicine* (New York: Academic Press, 2008).

[21] FDA Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products, U.S. Department of Health and Human Services, 1998.

[22] Concato, J., Shah, N., & Horwitz, R. I., Randomized, controlled trials, observational studies, and the hierarchy of research designs, *The New England Journal of Medicine, 342(25)*, 2000, 1887–1892.

[23] Miller, F. G., & Joffe, S., Equipoise and the dilemma of randomized clinical trials, *The New England Journal of Medicine, 364(5)*, 2011, 476–480.

[24] Downing, N. S., Aminawung, J. A., Shah, N. D., Krumholz, H. M., & Ross, J. S., Clinical Trial Evidence Supporting FDA Approval of Novel Therapeutics, 2005–2012, *The Journal of the American Medical Association, 311(4)*, 2014, 368–377.

[25] Roever, L., Endpoints in Clinical Trials: Advantages and Limitations, *Evidence Based Medicine and Practice, 1(2)*, 2016, e111.

[26] FDA Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs & Biologics, U.S. Department of Health and Human Services, 2007.

[27] Katz, R., Biomarkers and Surrogate Markers: An FDA Perspective, *NeuroRx, 1(2)*, 2004, 189–195.

[28] Cockburn, I. M., & Henderson, R. M., Absorptive Capacity, Coauthoring Behavior, and the Organization of Research in Drug Discovery, *The Journal of Industrial Economics*, *46*(2), 1998, 157–182.

[29] Higgins, M. J. and Rodriguez, D., The outsourcing of R&D through acquisitions in the pharmaceutical industry, *Journal of Financial Economics, 80(2)*, 2006, 351–383.

[30] Chan, T., Nickerson, J. A., & Owan, H., Strategic Management of R&D Pipelines with Co-specialized Investments and Technology Markets, *Management Science, 53(4)*, 2007, 667–682.

[31] Cohen, J., Gangi, W., Lineen, J. & Manard, A., Strategic Alternatives in the Pharmaceutical Industry, Kellogg School of Management, Northwestern University: U.S. 2004. Retrived from: https://www.kellogg.northwestern.edu/research/ biotech/faculty/articles/strategic_alternatives.pdf. Accessed from 1 June to 25 June 2016.

[32] Grabowski, H., & Kyle, M., Mergers and Alliances in Pharmaceuticals: Effects on Innovation and R&D Productivity, in Klaus Gugler & Burcin Yurtoglu (Eds.), *The Economics of Corporate Governance and Mergers* (Cheltenham: Edward Elgar, 2008)

[33] Danzon, P. M., Epstein, A., & Nicholson, S., Mergers and acquisitions in the pharmaceutical and biotech industries, *Managerial and Decision Economics, 28(4-5)*, 2007, 307–328.

[34] CenterWatch, Troubling numbers for big pharma consolidation, *In Vivo, 18(7)*, 2000, 2–3.

[35] Tjandrawinata, R.R. and Simanjuntak, D.G., The Impact of Mergers and Acquisitions in Research-Based Pharmaceutical Companies on Productivity, Department of Business Development, Dexa Medica Group, Jakarta, Indonesia, 2012. Retrieved from SSRN: http://ssrn.com/abstract=1981889.

[36] Simanjuntak, D.G. and Tjandrawinata, R.R., M&A of Generic Pharmaceutical Companies Increases Productivity, Department of Business Development, Dexa Medica Group, Tangerang, Indonesia. 2011. Retrieved from SSRN: http://ssrn.com/abstract=1946761.

[37] Rothaermel, F. T., Complementary assets, strategic alliances, and the incumbent's advantage: an empirical study of industry and firm effects in the biopharmaceutical industry, *Research Policy*, *30*, 2001, 1235-1251.

[38] Danzon, P. M., Nicholson, S., & Pereira, N. S., Productivity in pharmaceutical-biotechnology R&D: the role of experience and alliances, *Journal of Health Economics, 24(2)*, 2005, 317–339.

[39] Grabowski, H., Patents and New Product Development in the Pharmaceutical and Biotechnology Industries, No 02-25, Working Papers, Duke University, Department of Economics, 2002. Retrieved from: http://EconPapers.repec.org/RePEc: duk:dukeec:02-25. Accessed 25 June 2016.

[40] A Congressional Budget Office Study, Research and Development in the Pharmaceutical Industry, Congress of the United States, Congressional Budget Office, 2006.