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FDA Drug Approvals:
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We investigated the stock price behavior of public pharmaceutical and biotechnology companies upon approval of a drug by the Food and Drug Administration (FDA). Using event study methodology, we examine the reaction caused by the approval, separating it from the asset price movements caused by other factors such as market and industry effects. The results are then used to validate the model developed in this article as an alternative to the explanations given by Sharma and Lacey (2004). The results of this study support the Efficient Market Hypothesis, i.e. that the market reacts to the new information quickly and clearly.

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Introduction

The purpose of this article is to investigate the stock price behavior of exchange listed pharmaceutical and biotechnology companies at and around the time of the approval of a drug by the Food and Drug Administration (FDA). Using event study methodology we try to extract the reaction caused by the drug approval, separating it from the asset price movements caused by other factors, such as market and industry effects. To do so we rely on the Efficient Market Hypothesis formulated by Fama (1970, p. 383) implying that "security prices at any time 'fully reflect' all available information." Thus, any new information should be reflected in the stock prices immediately. Assuming the existence of the semi-strong form of market efficiency, we expect the reaction to the approval to happen on the approval day and on the following two days. In addition to the tests for quick reactions to the approval, we also develop a valuation model based on rational assumptions.

For a better understanding of our study we first describe briefly some important steps for drug development in the biotech and pharmaceutical industries. In general, the drug development process can be split up into five different stages: The preclinical phase, the first, second and third clinical study, and the NDA submission phase. In the preclinical phase, compounds are tested in vitro, i.e. in cells and on animals. If the results are positive, the company then decides to proceed with further tests. To do so, the company is obliged by Public Law 87-781 to file an Investigational New Drug Application (IND) with the FDA. If the company does not receive a clinical hold within 30 days of filing the IND, it can start with the clinical trial phase. In the first clinical study, the drug is tested on around 100 healthy test persons. If these tests are successful, the company can start with the second clinical study, in which the drug is tested on 200-300 test persons with the illness the drug is designed to address. In the third clinical study, tests are conducted on a much larger group of up to several thousand patients. Once the company determines that the results prove the drugs' effectiveness, it can compile the collected data to then file a New Drug Application (NDA) or a Biological License Agreement (BLA) with the FDA.[1] The NDA submission phase is the last step resulting in approval or rejection of the drug for marketing in the United States.

This drug development process takes a very long time. From the beginning of the preclinical phase to approval of a drug it takes an average of about 12 years.[2] Figure 1 shows how much time it takes on average to pass through the different stages.

Figure 2 shows that out of 250 drugs entering preclinical trials only one gets approval. Considering all drugs entering the clinical phases, only 1 out of 5 drugs will make it to approval.

There are several estimates concerning the financial resources needed to bring a drug to market.[3] The most recent study was conducted by (DiMasi et al. (2003)), who estimated the overall cost at US$ 802 million[4] for a new drug. About US$ 80 million[5] was out of pocket expenses. Another US$ 323 million was due to low success rates. The remainder, US$ 399 million, was for costs of capital using an average Return on Equity of 11%.

Once a drug is approved, it is patent protected for 17 years from the day the company applied for the patent, which usually is done when the drug has been identified (end of preclinical testing). Considering the time needed to get drug approval, only 10 years of effective patent protection typically remain. During that time the company must recover its

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[1] In the following, NDA will stand for both applications.
[2] See DiMasi et al. (2003).
[3] See Hansen (1979), DiMasi et al. (1991), Wiggins (1987), and Grabowski and Vernon (1990).
[4] All cost estimates are in 2000 US$.
[5] Authors' own estimate calculated with estimates obtained from DiMasi et al. (2003).

costs and make its profits, because after a patent expires other companies will soon offer a generic version at a lower cost, and cash flow will decrease quickly.

Drug companies are always in need of new revenue sources to offset the reduction in cash flow due to drug patent expirations. Therefore, one of the biggest challenges for biotech and pharmacological companies is to invest the positive cash flows from successful drugs in new drug developments and simultaneously manage the development process efficiently to obtain approvals for new drugs. Therefore, the moment of approval is a very important milestone in the history of a company, recognizing the past research efforts and assuring a monopoly to market the developed drug for a certain period.

So far only four case studies have been published concentrating on the biotech and pharmaceutical industries. Bosch (1994) investigated the FDA decisions published by the *Wall Street Journal* from 1962 to 1989. Bosch (1994) found significant reactions for t=-1 and t=0 (the day before and the day of publication respectively).

Deeds et al. (2003) investigated the effect of drug rejections on the applicant company. Covering the time period from 1992 to September 2002, they were able to identify 55 drug rejections and found a strong abnormal reaction to the event of -20% on average, strongly supporting the existence of negative abnormal returns to the event.

Sharma and Lacey (2004) analyzed the effect of both approvals and rejections of pharmacological drugs by the FDA. Their sample of "approvals" included 344 drugs and the sample of "rejections" included 41 drugs. They found that both the "approval" and the "rejection" events were efficiently incorporated into the stock price of the firms, showing strong positive abnormal returns for approvals and strong negative abnormal returns for rejections. The reaction to approval was significant for the days t=-1, t=0 and t=1. No significant reactions were observed before or after this period. The same results were found for rejections. Furthermore, the average reaction to approval in t=-1 to t=1 was 1.56%, compared to -21.03% for rejection. These results therefore showed that rejections produce much greater financial losses than the gains attributable to approvals.

Sarkar and de Jong (2006) investigated announcement effects at four points in the FDA review process and how investors react. Their sample included both large and small pharmaceutical firms, but they did not make a distinction between biotechnology and traditional pharmaceuticals. In regard to the 'approval' event they observed statistically significant positive reactions on the event day and the day after. In the case of rejection a clear negative reaction to the announcement on the event day was registered.

In the following section, we will give an overview of the data used in our study and of how we analyzed them. In Section 3 we will first test whether market efficiency in its semi-strong form can be assumed. Second, we will present our valuation model, and derive and test two hypotheses. The final section summarizes our findings.

I. Data and Methodology
A. Data
Pharmaceutical drug approvals

In the time period 1985 to 2004, all pharmaceutical drug approvals defined as New Chemical Entities by Tuft´s CSDD were identified. In total, the FDA approved 487 drugs during this 20-year period. These 487 drugs were developed by 93 different companies. As shown in Table I, 218 drugs from 47 companies were finally included in the case study. In the case of S&P Composite Index, Datastream only delivered the index starting from January 1, 1988. Therefore, another 22 approvals had to be excluded for the analysis using the S&P Composite Index in the market and index model.

Biotech drug approvals

Biotech approvals in the context of this paper are defined as drugs listed as "Important Biological Drugs" in the annual summary of "The Pink Sheet".[6] In the case of S&P Composite Index, Datastream only delivered the index starting from January 1, 1988. Therefore, a further approval had to be excluded for the analysis using the S&P Composite Index in the market and index model. The sample size is shown in Table II.

Stock market data

The relevant data for each company were retrieved from the Datastream database. In the case of stock listings in currencies other than US dollars, the data were converted into US dollars using the exchange rates provided by Datastream.

B. Methodology

Two event studies were conducted using the Market Model and the Index Model. For the Market Model, the SNP Composite was used as Market Index and the necessary coefficients were estimated for each drug approval by running OLS regressions separately. For the Index Model either the World DS Biotech Index or the World DS Pharmaceutical Index was used as a benchmark. Details about the event study methodology deployed are described in Appendix 1. The Index Model and Market Model were both used to calculate ARs and APIs for the Biotech Approvals and the Pharmacological Approvals.

II. Empirical Results
A. Market Efficiency

Similar to Sharma and Lacey (2004), we tested market efficiency with regard to the approval event. In addition to the pharmacological approvals we also added the biotech approvals to see if there were any differences in the reaction patterns between biotech approvals and pharmacological approvals. In contrast to Sharma and Lacey (2004) and Sarkar and de Jong (2006), we followed the results found by Boehmer et al. (1991) suggesting the use of varying standard deviations for each day in the event window, since that improved the robustness of the t-statistics. The following hypothesis was tested:

H 1: The approval event results in a positive abnormal return for the applicant company.

On a daily basis, highly significant abnormal returns[7] can be observed in t=-1 for biotech and t=-2 and t=1 for pharmacological approvals. The API also shows highly significant positive abnormal returns starting from day -1 for the biotech approvals and 2 days later (t=1) for the pharmacological approvals. In Tables III and IV we present the results:

In Figure 3, one can see that the reaction to the approval happens within a few days of the approval. Thereafter no large changes are shown.

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[6] The Pink Sheet is a well-known monthly biotech/pharmaceutical publication summarizing the most important developments in the drug discovery process. In the annual summary the Pink Sheet publishes a list of "Important Biological Drugs". Due to the lack of other objective criteria to sort out biological approvals (the FDA does not publish sufficient data) we felt comfortable using these annual summaries.

[7] The asterisks stand for different significance levels: * for alpha=0.10, ** for alpha=0.05 and *** for alpha =0.01.

Comparing biotech and pharmacological indices we observed a stronger positive API for the Biotech approvals.

Results for the Market Model in Table V on a daily basis show highly significant abnormal returns in t=-3, t=-1 and t=0 for the biotech approvals, whereas for pharmacological approvals a significant abnormal return can only be registered at t=1. With a p value of 0.0017, however, it is highly significant.

For the biotech approvals, the API also shows highly significant positive abnormal returns starting from day -1 (see Table VI). Pharmacological approvals yield similar results although not that strong (see Table VI): The Market Model also shows significant abnormal reactions for the periods t=-2 to t=2 (biotech) and t=-2 to t=1 (pharmacological). It can be stated that the Index Model and the Market Model deliver very similar results both strongly supporting H1.

We have chosen a more conservative approach than Sharma and Lacey (2004) to take account of confounding events, i.e. excluding more companies from the original sample. With samples of 68 for biotech and 218 for pharmaceutical, the number of approvals entering the study is still sufficiently large. By including the biotech approvals, we were able to extend the research to the biotech industry. Comparing the results with the findings of Sharma and Lacey (2004) we come up with very similar results for the abnormal returns. Calculating the simple sums of the abnormal returns for the period from t=-3 to t=3 for the pharmaceutical approvals as an approximation, Sharma and Lacey (2004) registered an abnormal return of 1.76 % versus 1.70 % in our study (see Table VII).

Taking a closer look at the Sharma and Lacey results, we found that they left the standard deviation unchanged at approximately 0.02261 (our estimation from their data), whereas our results suggest quite substantial changes in the standard deviation, especially during the approval day. Since the change mainly occurs in t=0, it is very probable that this is caused by the approval itself. Therefore, we feel more comfortable controlling for the standard deviation changes by using the test statistics presented in Appendix 1. However, if we use the same constant standard deviation as Sharma and Lacey (2004), we find very similar results (as shown in Table VII column `Statistic adj`). The differences in the example above become very large in t=0, since we record an increase in standard deviation from 0.025 to 0.061. Using the method employed by Sharma and Lacey (2004), we would get a highly significant abnormal return (p=0.0068), whereas our method and data do not show any relationship. [8]

We believe our approach of allowing changes in standard deviation to be a more conservative approach since we register very significant changes in the standard deviation (in many cases a tripling), especially on t=0 and t=1. But even with standard deviation changes, we still show significant relationships.

The second hypothesis tested was as follows:

H 2: From t=4 to t=20 no significant abnormal return can be observed.

Biotech approvals

Like H1, H2 was tested with the Index Model with World DS Biotech Index and the Market Model with SNP Composite Index. The API was calculated from t=4 up to t=20. The results are printed in Appendix 2 and Appendix 3. For both alternative models the result is clear: There is no significant evidence of abnormal returns, either positive or negative.

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[8] Sarkar and de Jong (2006) yield similar results to us, even though the two studies are not particularly comparable due to differences in the databases.

Pharmaceutical approvals

Pharmaceutical approvals deliver the same results as the biotech approvals. As shown in Appendix 4 and Appendix 5, there is no significant positive or negative abnormal return in the post-announcement period.

Summarizing the tests for market efficiency we can state the following:

Biotech drugs

For the biotech approvals, stock prices react to the event in a semi-strong form. There is a slight tendency towards the strong form of Market Efficiency though, since a good part of the abnormal reaction already happens on day t=-1. If we take the API over t=-2 to t=2 we get a positive reaction of 2.94% (Index Model) or 2.40% (Market Model), making it highly significant (p=0.0084 for the Index Model and p=0.0028 for the Market Model). Expressing the reaction on t=-1 as a percentage of the API, we show changes of 30.70% (Index Model) and 41.35% (Market Model) one day before the approval becomes public knowledge. On t=0, the market again reacts very strongly to the approval with average abnormal gains of 0.74% (p=0.063) for the Index Model and 1.53% (p=0.020) for the Market Model. One reason for the reaction before the approval becomes publicly known could be insider trading, of course. But it is also possible that the approval day was not correctly specified in our study – perhaps the CEO made a public announcement concerning the approval before the actual event, for example.

Pharmaceutical drugs

The event is efficiently incorporated into the stock prices in a semi-strong form. We find a highly significant abnormal return only at t=1 for both models (p=0.0023 for the Index Model and p=0.0017 for the Market Model). For the period from t=-2 to t=2, the changes in APIs are also highly significant at p=0.010 and p=0.026. Regarding the post-announcement window, there is no significant trend (defined as p<0.10) towards positive or negative abnormal returns in either model. In summary, for the pharmaceutical approvals we find strong support for the existence of an efficient market in a semi-strong form.

B. Our Valuation Model

In their interpretation, Sharma and Lacey (2004, p. 304) concluded that "if the rewards for success are significantly smaller in magnitude than is the punishment for disappointment, the decision to initiate and then to continue new product development initiatives is likely to be a difficult one for firms." Their conclusion built on the assumption that all the approval-induced abnormal returns were covered within the event window. The results of their study were not at all contradictory. Within the event window there was only a clean, quick and significant reaction in t=-1, t=0 and t=1. All other average daily abnormal returns were insignificant.

However, we would like to suggest a different way of looking at the discrepancy of the absolute abnormal return occurring between "rejections" and "approvals". As an example, let us assume company A has a drug in development. The net present value of that drug given approval is US$ 1 billion.[9] Since the drug has already passed the first and second phase, the probability of approval is already fairly high at, let us say, 60%. This would suggest that the

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[9] The NPV is assumed to reflect also the specific risk connected to the development process by an adequate premium in the discount rate.

drug already contributes US$ 600 million to the market capitalization of the stock.[10] If the company passes the third phase and enters into the approval phase, the market would increase the approval probability up to, let us say, 80 %, resulting in an abnormal increase of market capitalization of US$ 200 million. This example shows that one should observe a continuous increase in the cumulated average abnormal return over the drugs which we know will get approval. But even drugs that are not approved but have accomplished one phase and enter the next, will have an increase in the expected value priced in the market capitalization. Since the historical approval probability for drugs entering the NDA submission is already very high (around 83%, to take the average put forward in DiMasi (2001, p. 294)) for the early '80s to early '90s), a large part of the value of the drug if approved has already been anticipated and built into the stock price, resulting in an abnormal return, as shown in Figure 4. Thereafter, Figure shows the reaction to approval. If the drug is approved, there will be a quick adjustment of the value of the drug, resulting in an increased abnormal return. After that, no abnormal returns should be observed. In the case of rejection (see
Figure 5), the market might have seen a few negative signs, but the company trying to get approval will not jeopardize its chances by publishing negative results as long as no decision has been made by the regulatory body. Thus, the market might anticipate some of the development, but a large part of the rejection will still come as a surprise. Once the news of a rejection comes out, the market will trade down the stock immediately, resulting in a negative abnormal return.

As we can see in Figure 4 and
Figure 5, following our argumentation it becomes clear that approvals result in a smaller abnormal return reaction – in absolute terms – than rejections. Therefore, we believe that it makes sense to take a look at the product development process as a whole. The mismatch observed between rewards of approvals versus the punishment of a rejection is simply because of the build-up of abnormal returns throughout the whole development process rather than just at the end, as suggested by Sharma and Lacey (2004).

Based on the argumentation above, we develop a model that we think should work well for drug approvals. First of all, we investigate drug approvals before and around the approval event since it is very difficult to filter the abnormal return of a drug throughout the whole development cycle, i.e. 12 years on average. Unfortunately, we were not able to collect data for rejections, but we believe that the results from the approvals already sufficiently support our model. In the following, we concentrate our study on the time-period in the gray box within Figure 4.

Before drugs can be approved by the FDA, the company applying has to submit a NDA. The average time from NDA submission to approval of drugs is 18.2 months. On average, 83 % of the drugs for which a NDA was submitted are approved.[11] We believe that the market participants use the average success factor to evaluate the chances of the average drug being approved and hence the average abnormal performance of each sponsor.

As shown in Figure 6, we believe that the market assumes some average approval probability for each drug, which increases over time.

The majority of this probability will be determined by historical approval probabilities and also drug specific factors. Conference presentations and/or published results of the drug will change the specific approval probability for each drug in some way.[12] So over time more

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[10] Assuming there is no unsystematic risk.
[11] See DiMasi et al. (2003).
[12] However no results from the official FDA approval process are published since that process is happening within the FDA and therefore is a "black box" for market participants and also the sponsors themselves.

and more information will become available. On average, this kind of positive news flow would mean a steady increase in the perceived probability of a drug's success, resulting in a positive average abnormal return in the approval phase.[13] However, uncertainty will still remain up to a point. This uncertainty immediately vanishes when the approval occurs. Thus, with approval there should be a final positive abnormal return if the remaining uncertainty is sufficient to move prices.

Taking a look at the development of returns from our sample 280 days before and after the approval, the charts for biotech and pharmacological approvals indicate that the slope changes around the time of approval (Figure 7 and Figure 8).

From these data we can draw the conclusion that the Market Model should be used with caution. When applying the Market Model one should be aware that the estimates of the Alpha and Beta coefficients[14] are biased in favour of a higher Alpha, leading to an underestimation (overestimation) of positive (negative) abnormal returns, especially for long-term event studies.[15] Therefore, we control for that potential error by using only the IM for long-term studies (H 3).

By calculating the API with an Index Model over a two-year period around the approval, we obtain Figure 10, API for an above-average NDA. As shown in Figure 9, there is a clear upward trend for the pharmacological approvals the year before the approval, and afterwards it remains much at the same level. The biotech approvals also show an upward movement of the API even though the sideward movement the year after shows a slightly downward trend.

To cross check, we also calculated the APIs for the MM. As results we get APIs of -1.17% (pharmacological) and -9.40% (biotech) for the year before the event as opposed to 19.84% and 8.22% for the IM. Given the above-mentioned bias through to an overestimation of Alpha, that difference was expected.

To see if our projection of the run-up - caused by an increase in the expected approval probability - is significant, we tested the following hypothesis:

H 3: From t=-280 to t=-3 a significant positive abnormal return can be observed.

Biotech
The IM shows no significant positive abnormal return. The absolute abnormal return of 8.22% over the period is quite large but not statistically significant. H3 is not supported for biotech approvals. (see Table VIII)

Pharmaceutical
Index Model with World DS Pharmaceutical Index (see Table IX)

With the Index Model, the API over t=-280 to t=-3 adds up to an abnormal performance of 19.84 %, which is statistically significant with p=0.029.

In addition, we differentiated between drugs with a long NDA period and those with a short one. Our assumption is that as time passes, more information will be provided by the company.

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[13] It is assumed that the information flow during the FDA approval phase is independent of the speed of the approval.
[14] Assuming that the estimation period is allocated before the approval.
[15] The average Alpha for daily returns, for example, was estimated at 0.06% or an annualized 16 %, clearly overestimating the risk free rate.

Taking only the subsample of drug approvals, news should be positive. The more positive news comes to the market, the higher the expected success rate will be. Therefore, we believe that there should be a clear difference between companies whose drugs were approved below the average time and those whose drugs were approved above the average approval time.

In the case of above-average approval time in 10, the positive news flow would continue, resulting in an even higher approval probability priced in. Still, uncertainty remains, leaving a small abnormal return on the approval day as shown in Figure 10.

As shown in Figure 11, in the case of below-average approval time, the market will be surprised by the early approval, which has not yet been expected or built into stock prices. In theory, this surprise effect should be reflected by a higher abnormal return than average in the approval window.

To test for differences between drugs with above-average versus below-average approval time, we derive the following hypothesis:

H 4: The observed abnormal returns around the approval should be larger for companies with drugs with below-average approval time than those with above-average approval time.

If our model holds, we should be able to see significant differences.

Biotech companies
Unfortunately, the necessary data for H 4 were not available for the biotech approvals, because they are not published by the FDA.

Pharmaceutical companies
In Table X, the results of drug approvals with below-average NDA times (short NDA) will be compared to those with above-average NDA times (long NDA).

Model with World DS Pharmaceutical Index
Using the Index Model, it can be assumed that on average the short NDAs show significant positive APIs from t=-1 onwards. For the long NDAs, however, positive APIs are not statistically significant. The percentage changes speak for the short NDAs where 2.44% API from t=-2 to t=3, whereas the long NDAs register only 0.42% respectively as shown in Table XI.

Testing the two groups for differences for the period from t=-2 to t=3, the short NDAs have a significantly higher API than the long NDAs (p=0.048). As can be seen in Figure 12 and Table XII, there is clearly a higher performance in the period between t=-3 to t=3, where the reaction to the approval occurs. Thereafter, no large changes in the API are to be observed. Similar but weaker results can be achieved when we apply the Market Model. The short NDAs show a significant positive API (p=0.039) effect for the time period t=-2 to t=3, whereas the long NDAs do not show any effect as shown in Table XIII. The test of differences shows a weak tendency (p=0.084) for short NDAs to outperform long NDAs. The percentage difference adds up to 1.81% in t=3.

C. Sensitivity to outliers
Even though we felt quite confident with above results, since they were in line with the results of Sarkar and de Jong (2006) and Sharma and Lacey (2004), we tested the robustness of the above statistics by trying to control for the effects of outliers. Due to the larger sample size

we present in the following the results for the pharmaceutical events. The results are similar for the biotech sample.

The distribution for the APIs for the event window is exhibited in Figure 13. As one can see, there is a tendency toward positive outliers with APIs of above 20%. In the sample five observations have APIs of above 20%, whereas no negative API below -20% can be observed. Now the question is what would happen if one took the outliers out of the sample. The answer is given in Table XIV, where the statistics are calculated without the API outliers above 20% and below -20% and are compared to the original sample results. The result is quite clear: No significant positive API reaction remains.

Analyzing the five outliers, we find a simple explanation: At $4.21 billion, the average market capitalization of event sponsors that produced those outliers was about one sixth of the average market cap in the sample. Hence, due to basis effects, the API reactions will be higher by nature, assuming the same absolute reaction to the event. Therefore, the outliers are not really outliers in the statistical sense. They just occur due to the wrong method being applied. Consequently, it is preferable to investigate the absolute reaction as opposed to the relative. Calculations of the absolute API returns are shown in Table XV. Again, no significant abnormal reaction can be observed.

For the biotech event we obtain similar results (Table XVI): Former highly significant results vanish almost completely. Only in t=0 do significant reactions remain. These results show impressively the sensitivity of the applied test statistics to outliers, and calls into question the existence of abnormal reaction. It might well be that no reaction is observed after all.

D. Findings for our Valuation Model

Our Valuation Model shows support for H3 (testing for a significant abnormal return in t=-280 to t=-3) and H4 (testing for differences in abnormal returns depending on the length of the NDA submission period).

H3 can be supported for the pharmaceutical approvals. From t=-280 to t=-3 an API of 19.84% was registered (p=0.029). This clearly indicates that the market prices reflect information obtained over time, e.g. by presentations of drug results at conferences or company press releases (see Figure 6).

For the biotech approvals, no significant results were obtained. The reason for this could lie in high burn rates of money, that is, the gain within the NDA phase could be offset by a high negative cash flow. Another reason could be found in the more specialized approach of biotech drugs aiming for a certain segment, which does not allow above-market return even in the case of success since the potential profits with niche products in absolute numbers are much smaller than those of blockbusters.[16]

Testing H4, in the period t=-2 to t=3 for the Index Model we find a significantly higher API for the group with short NDAs than for the group with long NDAs (p=0.048). For the Market Model, we observe for the same period at least a tendency for the short NDAs to outperform (p=0.084). Our Valuation Model explains these results very well (see Figure 10 and Figure 11). Therefore, we see the difference between short and long NDAs as supporting our model.

Last but not least, the sensitivity of the above conclusions to outliers should not be underestimated. As is shown, taking away the outliers leads to an almost complete disappearance of significant reactions, questioning the conclusions of studies made up to now in that field. In general, for the drug approvals it seems more appropriate to look at the absolute

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[16] In return, those niche products (orphan drugs) should see a much higher approval rate.

API reactions rather than the relative reactions. Assuming the validity of our valuation model the only explanation would be an almost perfect anticipation of the approval by the market participants.

III.   Conclusions

In this research, we analyzed the event of drug approval separately for biotech and pharmaceutical drugs. Using Sharma and Lacey (2004) as a starting point, we developed an alternative evaluation model which explains the statistical and the industry specific properties for the event of drug approvals better (see   B. Our Valuation *Model*). The findings are as follows:

- A fast reaction to drug approval as expected by the Efficient Market Hypothesis for its semi-strong form can be observed for biotech and pharmaceutical approvals (see Figure 3).
- Biotech and pharmacological approvals show the same clear reaction patterns. The only noticeable differences are as follows: Biotech approvals already partly show a significant positive abnormal reaction in $t=-1$. The run-up we expected in our model the year before the approval proved to be true for the pharmacological approvals but was not significant for biotech approvals.
- Contrary to the findings of Sharma and Lacey (2004), whereby all the loss or gain of a new drug developed can be observed in the event window, we built an alternative model of how we think the market partly anticipates the approval. The results for H3 and H4 support the validity of this model for the pharmaceutical drug approvals.
- The Market Model should not be used in this kind of event study, since a clear regime switching takes place at or around the approval day (see Figure 7 and Figure 8).
- Standard deviations should be calculated on a daily basis since in $t=0$ a sharp rise occurs (see Table VII) resulting in a severe t-statistic bias overestimating the significance if the standard deviation is kept constant over the event window.
- Sensitivity to outliers is a hot issue and may not be factored out. In the case of drug approvals as an event it seems appropriate to use absolute APIs to avoid those "artificial outliers" produced due to an inadequate method.

Further research should be done testing the developed evaluation model on drug rejections. For example, it would be very interesting to study the differences in the pre-event window.

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Figure 1
Average duration for drugs to pass through different product development stages

Average duration for drugs to pass through different phases
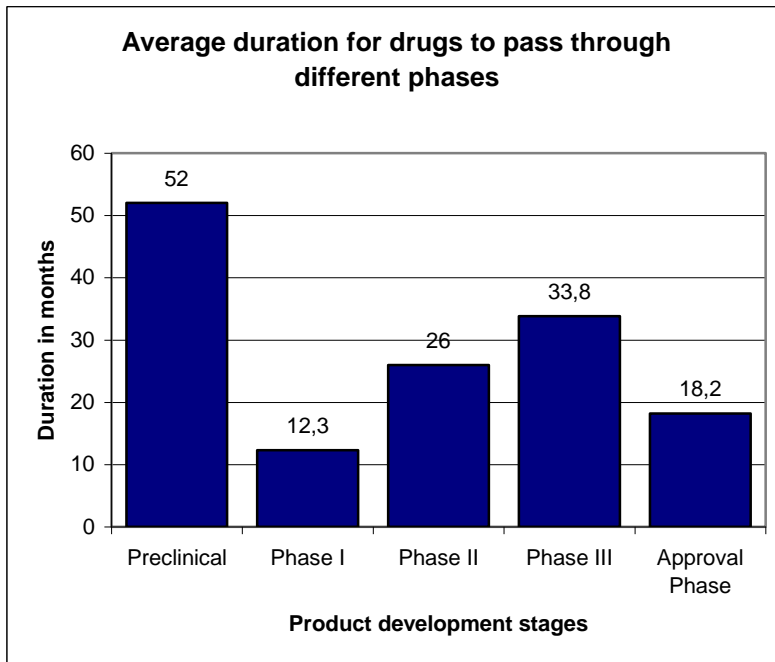
Figure 2
Fall-out probabilities

Fall-out probabilities from one stage to the next
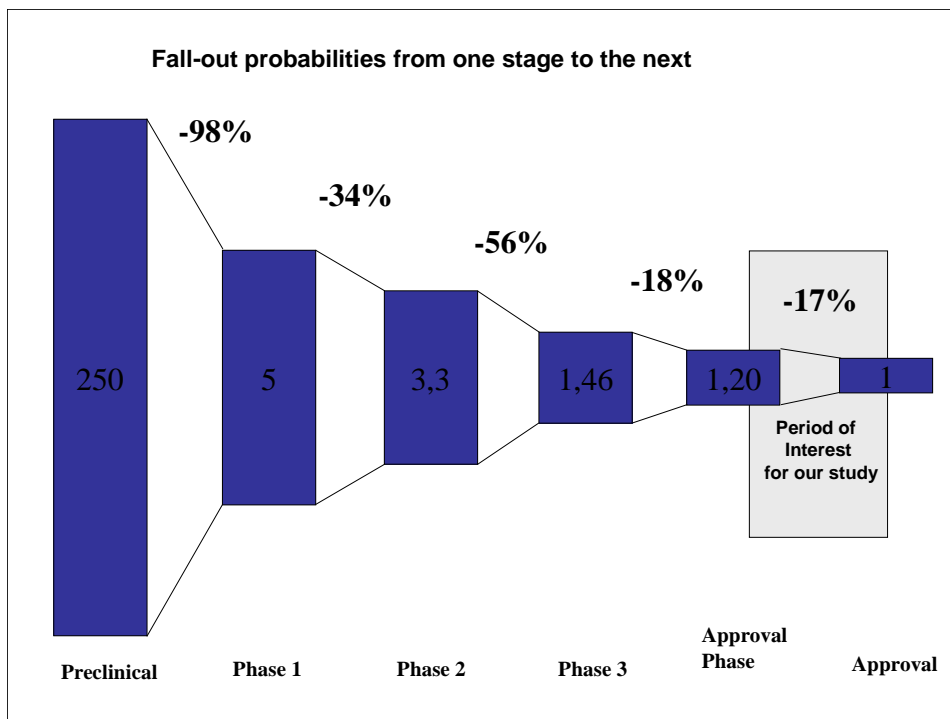
Figure 3
Biotech and pharmacological APIs for Index Model
with World DS Biotech/Pharmacological Index
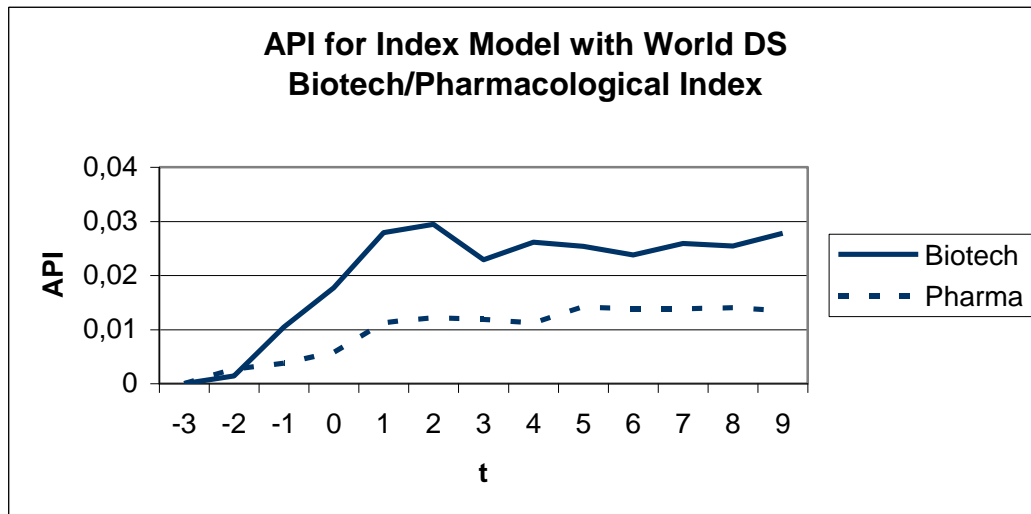
Figure 4
Expected reaction in the case of approval
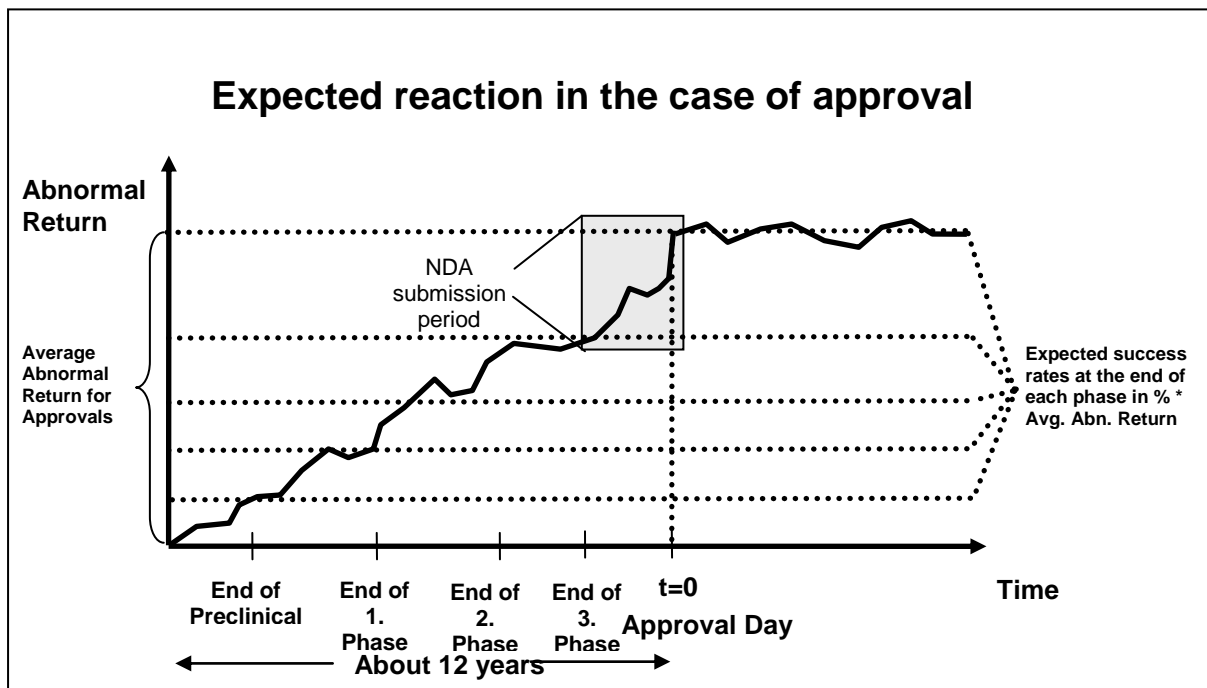
Figure 5
Expected reaction to rejections

Expected reaction in the case of rejection
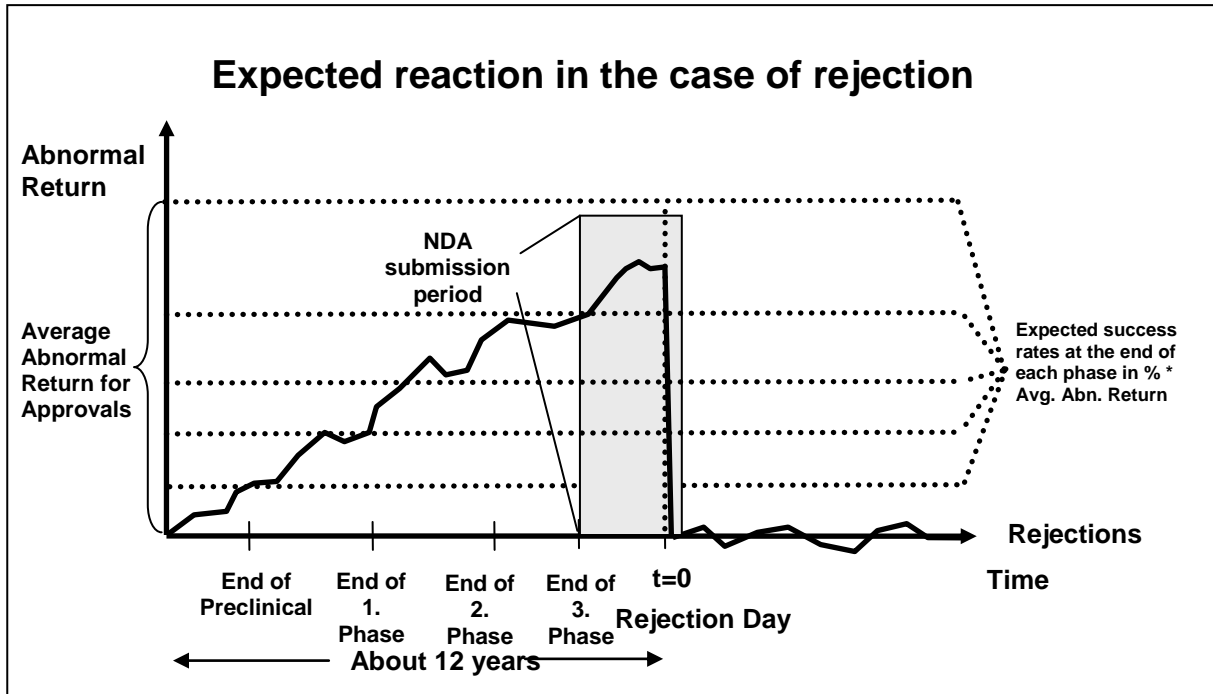
Figure 6
Expected price behavior within the NDA submission period
(see shaded box in Figure 5)
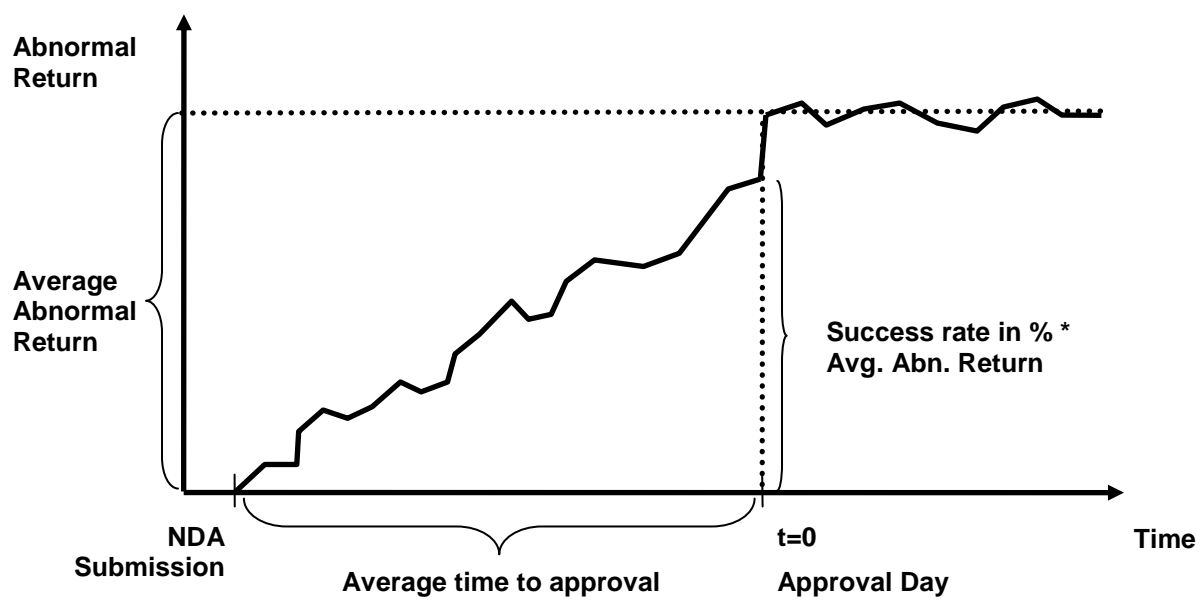
Figure 7
Comparison of the return for biotech one year before and after approval
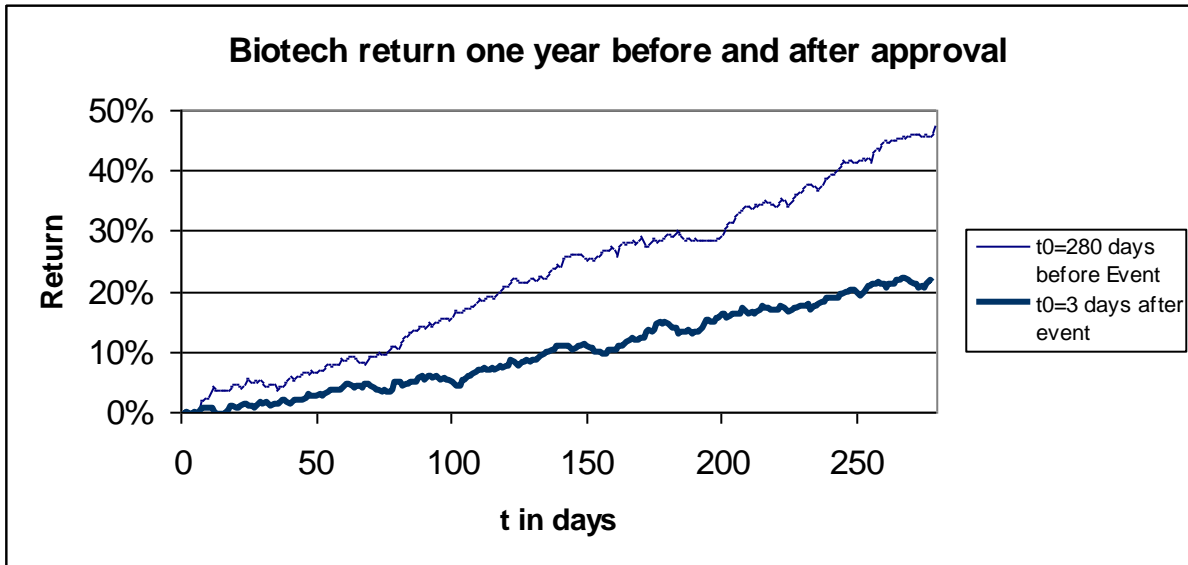
Figure 8
Comparison of the return for pharmacological one year before and after approval
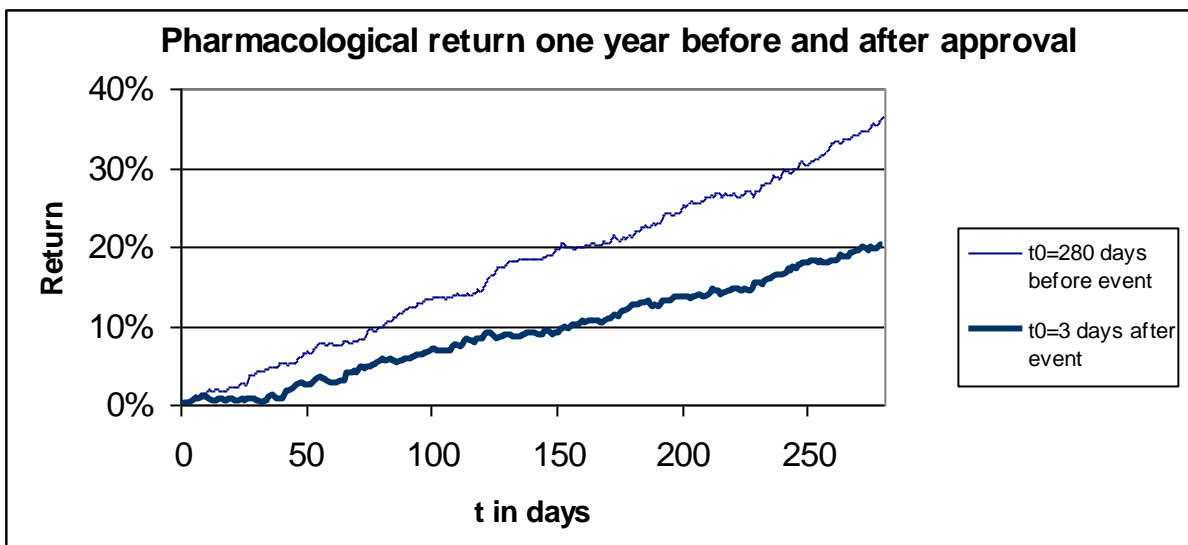
Figure 9
API for 280 days before and after the biotech and
pharmacological approvals for the Index Model
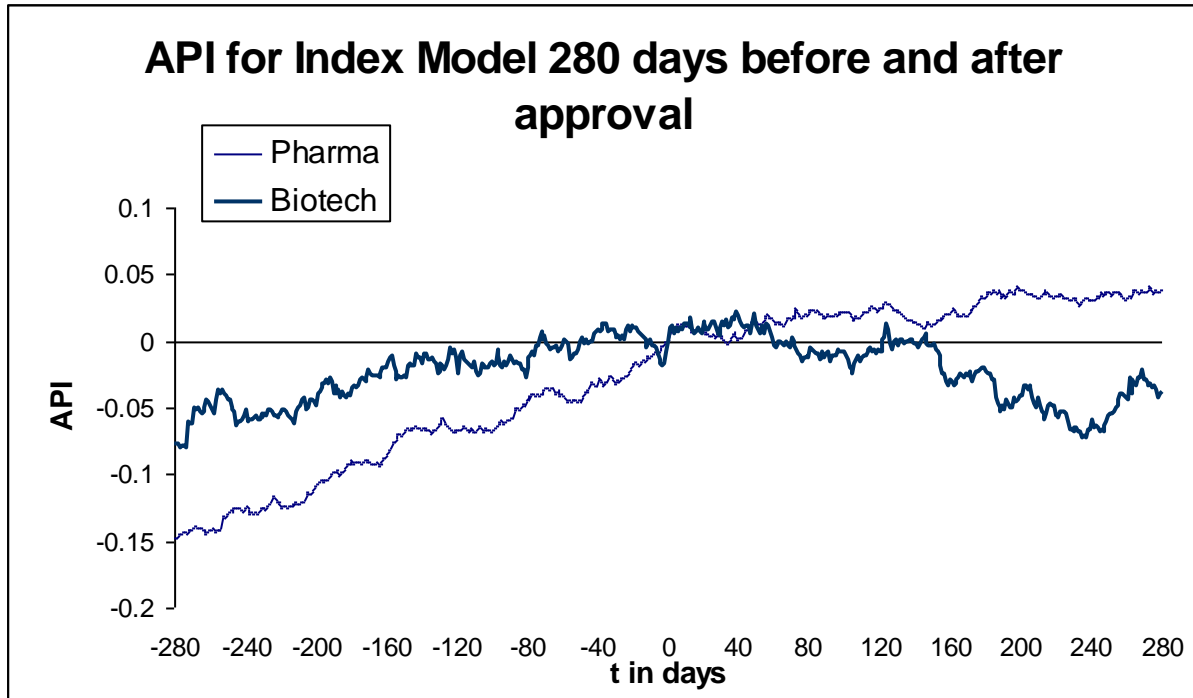
Figure 10
API for an above-average NDA
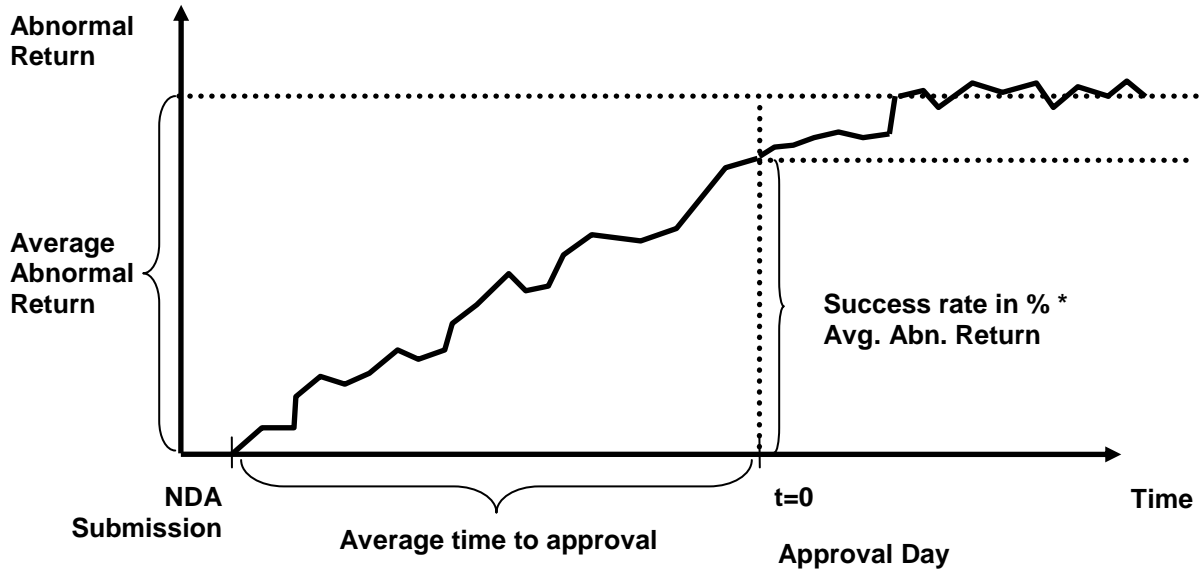
Figure 11
API for a below-average NDA

Abnormal
Return

Average
Abnormal
Return

Success rate in % *
Avg. Abn. Return

NDA
Submission

Average time to approval

t=0

Approval Day

Time
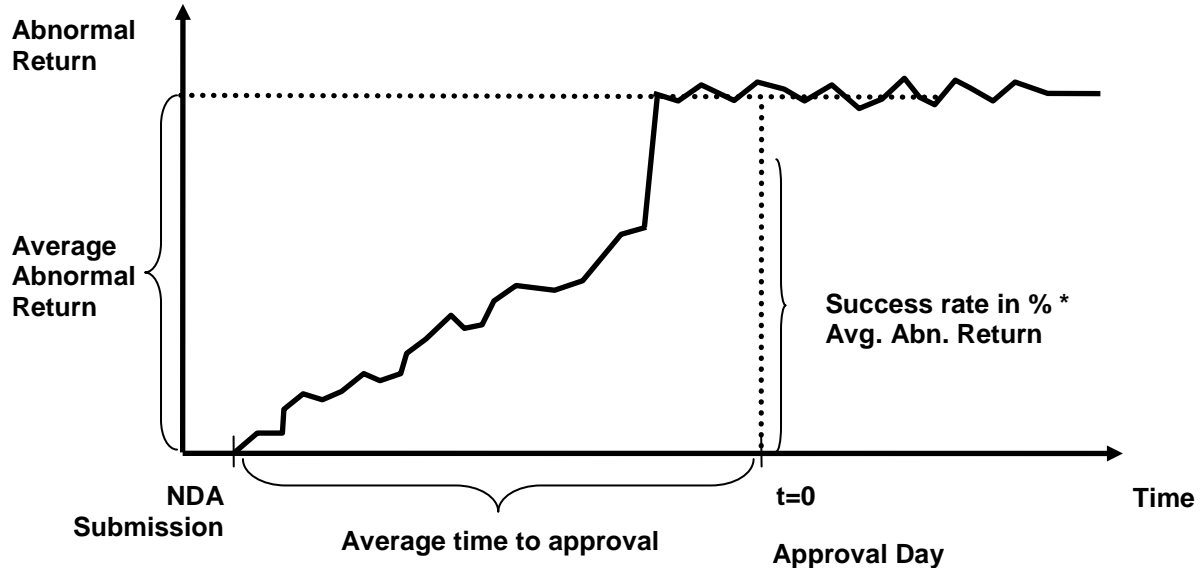
Figure 12
Out performance of API short NDA vs. API long NDA

API "short NDA" vs. "long NDA"

3,00%
2,50%
2,00%
1,50%
1,00%
0,50%
0,00%

API

-3 -2 -1 0 1 2 3 4 5 6 7 8 9

t
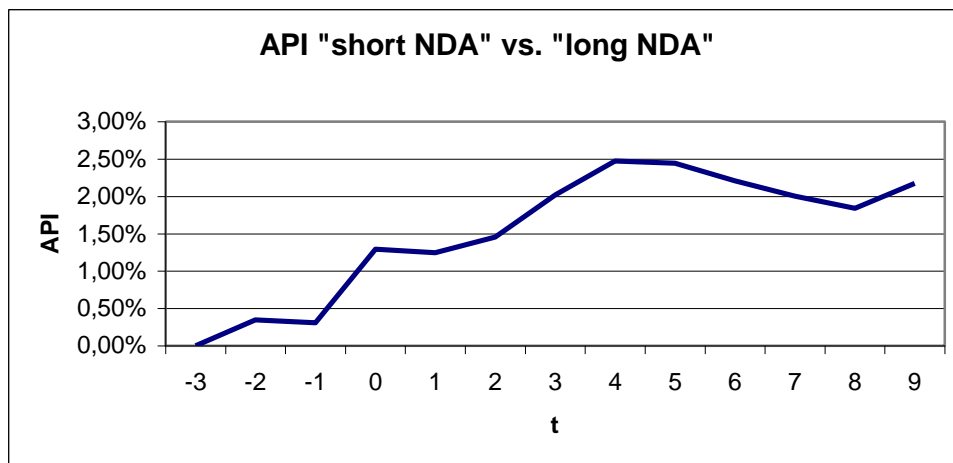
Figure 13
Distribution of APIs for pharma approvals
from t=-2 to t=3 based on the MM with S&P Composite as index
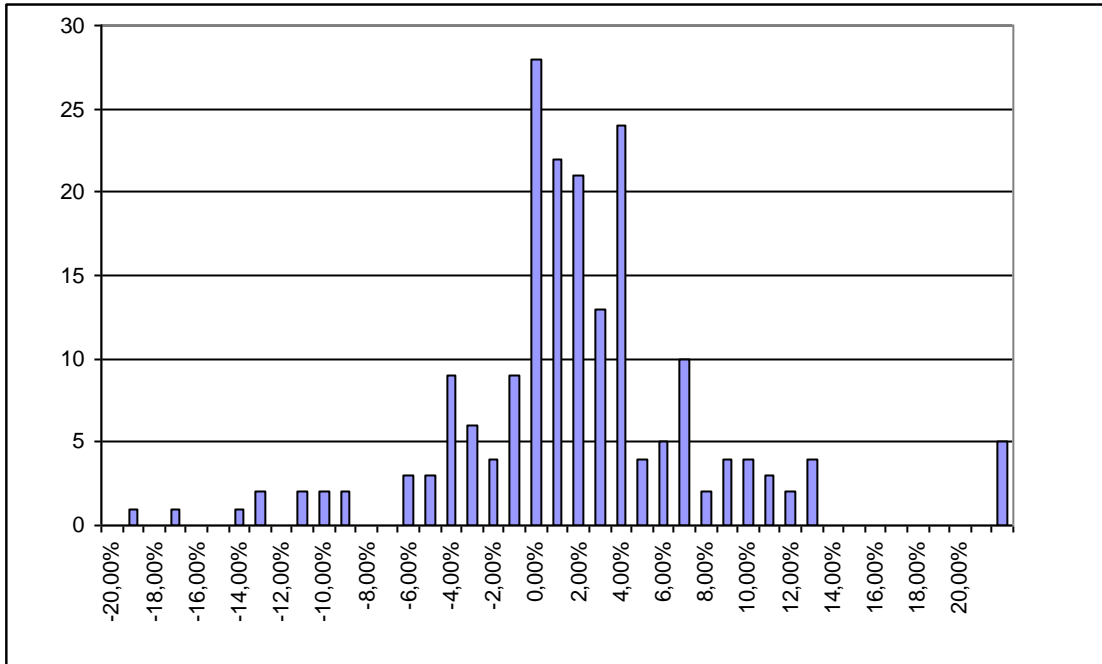
Table I
Pharmaceutical Sample Selection

Total drug approvals 1985-2004:	487
Deleted due to mergers & acquisitions:[17]	-29
Deleted due to drug approval within the same company:[18]	-130
Because the company was not publicly listed, or insufficient data before or after the approval date:[19]	-110
Drug approvals included in the event study:	218

Table II
Biotechnology Sample Selection

Total drug approvals 1985-2004:	109
Deleted due to mergers & acquisitions:[20]	-12
Deleted due to drug approval within the same company:[21]	-8
Drugs where the sponsor was not publicly listed, or insufficient data before or after the approval date:[22]	-21
Drugs included in the event study:	68

Table III
Biotech - ARs for Index Model with World DS Biotech Index
and World DS Pharmacological Index

	Biotech			Pharmaceutical		
t	Average AR	t-Statistic	N	Average AR	t-Statistic	N
-3	-0.185%	-0.683	68	-0.010%	-0.007	218
-2	0.144%	0.491	68	0.266%	1.301	218
-1	**0.902%**	**2.468*****	**68**	0.103%	0.642	218
0	0.735%	1.499*	68	0.245%	0.592	218
1	0.947%	1.267	68	**0.553%**	**2.753*****	**218**
2	0.121%	0.261	68	0.077%	0.437	218
3	-0.493%	-1.300*	68	-0.029%	-0.149	218

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[17] Drug approvals were taken out of the sample if the applicant company formed part of a merger or an acquisition activity up to two years before and six months after the merger or acquisition was announced to prevent confounding effects.

[18] A confounding effect was assumed to exist in the event of another drug approval within the same company six months before or three months after each approval.

[19] A minimum of data seven months before and after the approval was required to be included in the approval study.

[20] See footnote 8.

[21] See footnote 9.

[22] See footnote 10.

Table IV
Biotech - API for Index Model with World DS Biotech/Pharmacological Index

	Biotech			Pharmaceutical		
t	API	t-Statistic	N	API	t-Statistic	N
-2	0.144%	0.491	68	0.266%	1.301*	218
-1	**1.042%**	**2.292****	**68**	0.376%	1.366*	218
0	**1.771%**	**2.797*****	**68**	0.576%	1.319*	218
1	**2.793%**	**2.566*****	**68**	**1.128%**	**2.349*****	**218**
2	**2.944%**	**2.392*****	**68**	**1.221%**	**2.309****	**218**

Table V
Biotech/Pharmacological - ARs for
Market Model with SNP Composite Index

	Biotech			Pharmacological		
T	Average AR	t-Statistic	N	Average AR	t-Statistic	N
-3	**0.497%**	**1.815****	**67**	-0.112%	-0.755	196
-2	0.191%	0.571	67	0.208%	0.928	196
-1	**0.992%**	**2.582*****	**67**	0.077%	0.397	196
0	**1.533%**	**2.063****	**67**	0.242%	0.530	196
1	0.073%	0.168	67	**0.649%**	**2.928*****	**196**
2	-0.262%	-0.599	67	0,00%	0.003	196
3	-0.186%	-0.448	67	-0.237%	-1.224	196

Table VI
Biotech - API for Market Model with SNP Composite Index

		Biotech			Pharma	
T	API	t-Statistic	N	API	t-Statistic	N
-2	0.191%	0.571	67	0.020%	0.091	196
-1	**1.184%**	**2.333*****	**67**	0.293%	0.931	196
0	**2.753%**	**2.869*****	**67**	0.491%	1.000	196
1	**2.742%**	**3.058*****	**67**	**1.151%**	**2.106****	**196**
2	**2.397%**	**2.774*****	**67**	**1.166%**	**1.944****	**196**

Table VII
Comparison of the results for pharmacological approvals of Sharma/Lacey , 2004) and our study

	Sharma/Lacey , 2004)			This study			
T	AR	SD	Statistic	AR	SD	Statistic	Statistic Adj
-3	+0.0001	0.023	0.08	-0.0005	0.023	-0.37	-0.37
-2	0.0019	0.022	1.57	0.0036	0.032	1.70	2.47
-1	**0.0020**	**0.022**	**1.67****	0.0026	0.025	1.54*	**1.75****
0	**0.0048**	**0.023**	**3.91*****	0.0039	0.061	0.93	**2.47*****
1	**0.0088**	**0.023**	**7.22*****	**0.0058**	**0.030**	**2.84****	**3.70*****
2	0.0010	0.022	0.85	0.0012	0.026	0.66	0.78
3	-0.0010	0.022	-0.85	0.0004	0.031	0.20	0.28

Table VIII
Index Model with World DS Biotech Index

t	API	Statistic	N
-3	0.08219826	0.98732674	68

Table IX
Index Model with World DS Pharmaceutical Index

t	API	Statistic	N
-3	**0.1984**	**1.89****	**218**

Table X
Pharmaceutical: API for the group with below and above-average NDA

	short NDA			long NDA		
t	API	Statistic	N	API	Statistic	N
-2	0.0042	1.50*	96	0.0007	0.19	95
-1	**0.0066**	**1.65****	96	0.0035	0.82	95
0	**0.0151**	**1.72****	96	0.0021	0.54	95
1	**0.0188**	**2.05****	96	0.0064	1.45*	95
2	**0.0210**	**2.08****	96	0.0064	1.28*	95
3	**0.0244**	**2.18****	96	0.0042	0.88	95

Table XI
Test for Difference between ´short NDA` and
`long NDA´ , Index Model with World DS Pharmaceutical Index)

Test for Difference		
t	Delta API	Statistic
-2	0.0035	0.78
-1	0.0031	0.52
0	0.0129	1.34*
1	0.0124	1.22
2	0.0146	1.29*
3	**0.0202**	**1.66****

Table XII
Pharmaceutical: API for the group with below and
above-average NDA , Market Model with SNP Composite Index)

	short NDA			long NDA		
t	API	Statistic	N	API	Statistic	N
-2	0.0014	0.49	91	-0.0014	-0.32	78
-1	0.0025	0.56	91	0.0065	1.23	78
0	0.0110	1.16	91	0.0048	1.06	78
1	**0.0168**	**1.66****	**91**	**0.0094**	**1.79****	**78**
2	**0.0191**	**1.74****	**91**	0.0077	1.31*	78
3	**0.0207**	**1.76****	**91**	0.0026	0.43	78

Table XIII
Test for Difference between ´short NDA` and
`long NDA´ , Market Model with SNP Composite Index)

Test for Difference		
t	Delta API	Statistic
-2	0.0028	0.54
-1	-0.0040	-0.58
0	0.0061	0.58
1	0.0074	0.65
2	0.0114	0.91
3	0.0181	1.38*

Table XIV
Test Results for Hypothesis 1 without outliers

	IM			MM		
T	**API**	**t-statistic**	**N**	**API**	**t-statistic**	**N**
-2	0.00252	1.12	197	0.00020	0.09	196
-1	0.00375	1.19	197	0.00293	0.93	196
0	0.00609	1.27	197	0.00491	1.00	196
1	**0.01129**	**2.12****	**197**	**0.01151**	**2.11****	**196**
2	**0.01175**	**2.00****	**197**	**0.01166**	**1.94****	**196**
3	0.01033	1.64	197	0.00946	1.51	196
	IM ex outliers			MM ex outliers		
T	**API**	**t-statistic**	**N**	**API**	**t-statistic**	**N**
-2	0.00057	0.34	192	0.00006	0.04	191
-1	0.00077	0.32	192	0.00012	0.05	191
0	-0.00108	-0.44	192	-0.00183	-0.73	191
1	0.00376	1.15	192	0.00350	1.06	191
2	0.00334	0.95	192	0,00252	0.68	191
3	0.00016	0.04	192	-0.00045	-0.12	191

Table XV
Absolute APIs for Pharma with MM
and S&P Composite as index

T	Market model		
	API	t-statistic	N
-2	-80.8	-2.07**	196
-1	-84.1	-0.99	196
0	-146.3	-1.32	196
1	-68.4	-0.61	196
2	-1.8	-0.02	196
3	107.2	0.77	196

Table XVI
Absolute APIs for Biotech with MM and S&P Composite as index

T	Market model		
	API	t-statistic	N
-2	12.5	0.28	67
-1	111.4	0.96	67
0	118.0	1.77*	67
1	4.7	0.06	67
2	-51.5	-0.32	67
3	193.4	0.75	67

APPENDICES

Appendix 1
Methodology

Type of Event Study

Very similar to the methodology used by , Sharma and Lacey 2004), our study estimated market model parameters using a 140-day period , day -150 to -10). The six-day event window , day -2 through day +3) was followed by a post-announcement window , day +4 through day +20) for a check of abnormal returns out of the event window. The abnormal return $AR_{i,t}$ on day t for security i in the market model was calculated as follows:

$AR_{i,t} = R_{i,t} - E(R_{i,t})$ where $R_{i,t}$ is the observed return on day t for security i and $E(R_{i,t})$ is the expected return on day t for security i. The expected return was calculated as $E(R_{i,t}) = \alpha + \beta R_{m,t}$ where $R_{m,t}$ is the market return and α and β are the parameters obtained from the ordinary least square regressions $R_{i,t} = \alpha + \beta R_{m,t} + \varepsilon_{i,t}$ for each single security i.

The abnormal return $AR_{i,t}$ on day t for security i in the index model was simply obtained by $AR_{i,t} = R_{i,t} - R_{m,t}$.

In both the index and the market model, two indices were used as a reference index: The SNP Composite and the World DS Biotech in the case of biotech approvals or the World DS Pharmaceutical in the case of pharmaceutical approvals.

The Abnormal Performance Indices , APIs) were calculated by cumulating the daily abnormal returns as follows: $CAR_{t,t+k} = \dfrac{(\sum\limits_{i=1}^{N} \prod\limits_{K=t}^{t+k}(1+AR_{i,t})) - N}{N}$.

Test statistics:
The significance of daily ARs was determined by using an approximate Gaußtest. The test statistic used was as follows:

$$v = \frac{\overline{X} - \mu_0}{S} \sqrt{n}$$

with:

$$S = \sqrt{\frac{1}{n}\sum_{i=1}^{n}(X_i - \overline{X})^2}$$

The test statistic for the APIs was calculated as follows:

$$v = \frac{\overline{X}_{t_1-t_2} - \mu_0}{S} \sqrt{n}$$

with:

$$S = \sqrt{\frac{1}{n} \sum_{i=1}^{n} (X_{t_1-t_2,i} - \overline{X}_{t_1-t_2})^2}$$

Tests for differences between two samples were conducted by using the test statistic shown below:

$$v = \frac{\overline{X} - \overline{Y}}{\sqrt{\dfrac{S_x^2}{n_1} + \dfrac{S_y^2}{n_2}}}$$

with:

$$S_x^2 = \sqrt{\frac{1}{n_1} \sum_{i=1}^{n_1} (X_i - \overline{X})^2}$$

$$S_y^2 = \sqrt{\frac{1}{n_2} \sum_{i=1}^{n_2} (Y_i - \overline{Y})^2}$$

With N>30 all three test statistics are approximately N, 0;1) distributed.

Appendix 2
Biotech: API for Index Model with World DS
Biotech Index from t=4 up to t=20

T	API	SD	Statistic
4	0.0032938	0.0357322	0.7601365
5	0.00246249	0.04202164	0.4832315
6	0.00112846	0.04274508	0.21769893
7	0.00318784	0.04704255	0.5588056
8	0.00272129	0.06342452	0.35381186
9	0.00577399	0.06491819	0.73343927
10	0.00559157	0.05939796	0.77627735
11	0.00528133	0.06618531	0.65315981
12	0.00230722	0.06303489	0.299602
13	0.00838535	0.06090219	1.12700402
14	0.00148472	0.07196634	0.16886969
15	-0.0006414	0.083153	-0.06313774
16	-0.00028715	0.0853144	-0.02755004
17	0.0018705	0.08938516	0.17128943
18	-0.00160225	0.08905963	-0.14726103
19	-0.00235587	0.09084461	-0.21227048
20	0.00504764	0.09991365	0.4135243

Appendix 3
Biotech: API for Market Model with SNP
Composite Index from t=4 up to t=20

T	API	SD	Statistic
4	0.00415467	0.03395976	1.0014049
5	0.00229021	0.04090396	0.4582979
6	-0.00037429	0.04084743	-0.07500423
7	0.00237333	0.04627718	0.41978643
8	0.00286914	0.06324227	0.37134822
9	0.00802345	0.06590549	0.99649924
10	0.00895171	0.06878165	1.06529724
11	0.00898013	0.07460512	0.9778808
12	0.00648967	0.07387722	0.7136482
13	0.00743566	0.07161925	0.84345425
14	0.00031666	0.07976788	0.03225083
15	-0.00097012	0.09212137	-0.08555347
16	-0.00170964	0.09148763	-0.15181477
17	-0.00073925	0.09099716	-0.06599893
18	0.00234656	0.09279277	0.20544202
19	0.00366756	0.09397335	0.31706185
20	0.00704661	0.09688227	0.59089183

Appendix 4
Pharmaceutical: API for Index Model with World DS
Biotech Index from t=4 up to t=20

T	API	SD	Statistic
4	-0.00060083	0.02622372	-0.33828468
5	0.00266748	0.03468415	1.1355311
6	0.00224467	0.04031301	0.82212119
7	0.00238266	0.05127921	0.68603922
8	0.00229876	0.05661177	0.59953457
9	0.00189351	0.05846331	0.47820191
10	0.00164262	0.06685662	0.36276231
11	0.0027836	0.07265462	0.56568183
12	0.00242356	0.07797399	0.45891453
13	-0.0014981	0.08045382	-0.27492925
14	-0.00118436	0.08117757	-0.2154141
15	-0.00123529	0.0787231	-0.23168313
16	-0.00035374	0.08607953	-0.06067468
17	-0.00033504	0.09211033	-0.05370596
18	-0.00011751	0.09808474	-0.01768886
19	-0.00129118	0.09650962	-0.19753589
20	-0.00263397	0.09862472	-0.39432457

Appendix 5
Pharmaceutical: API for Market Model with SNP
Composite Index from t=4 up to t=20

t	API	SD	Statistic
4	-0.00191578	0.02660752	-1.01058721
5	0.00126956	0.03546156	0.50249016
6	0.00347558	0.04168878	1.17015075
7	0.00478684	0.05332477	1.25994796
8	0.00578505	0.05842443	1.389779
9	0.00600541	0.06128005	1.37548811
10	0.00488027	0.06990208	0.9799125
11	0.00308435	0.07393908	0.58549505
12	0.0011201	0.08017053	0.19609823
13	-0.00198815	0.08310719	-0.33577203
14	-0.00267063	0.08665336	-0.43257522
15	-0.00392698	0.08638772	-0.6380289
16	-0.00248786	0.09122383	-0.38278171
17	-0.00401763	0.09503385	-0.59336817
18	-0.00505148	0.09931635	-0.71388884
19	-0.00628632	0.09978462	-0.88423188
20	-0.00819999	0.10423921	-1.10411804