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Analysis of stock market reactions to FDA and EMEA announcements

Thesis submitted in fulfilment of the requirements for the degree of

Master of Science in Economics

Joachim De Schrijver

supervised by

Dr. Dries Heyman

PREFACE

Writing the thesis is the final stage of a long journey towards obtaining the Masters degree. For me personally, it has been quite an exciting journey, especially a tough one as I combined obtaining my degree in economics with obtaining a PhD in Applied Biological Sciences. However, this would not have been possible without the continuous support of some important people.

First of all, I want to thank Ghent University for offering the flexible study programs which allowed me to combine both. I also want to thank my PhD promoter, Prof. Wim Van Criekinge for giving me the flexibility to attend some classes, attend exams, and allow me to schedule my own agenda. Furthermore, I also want to thank my fellow students for understanding my situation and being there when I needed yet another syllabus or needed to reschedule meetings when I was unable to attend them. And last but not least, I want to thank my friends and family for their continuous support throughout the recent years.

I want to thank Dr. Dries Heyman for the opportunity to study the stock price responses of biotech and pharmaceutical companies in response to regulatory decisions. This research question has been intriguing me for quite some time and through this thesis I finally was able to investigate this and combine my different interests in both life science and capital markets.

I had a wonderful time conducting the research and really enjoyed writing this thesis. I hope you will have an equally great time reading this thesis.

Joachim De Schrijver Ghent, May 2013

Contents

LIST OF ABBREVIATIONS

AMEX	American Stock Exchange
API	Application Programming Interface
BLA	Biologic License Application
BTM	Book-to-market
CAPM	Capital Asset Pricing Model
CHMP	Committee for Medicinal Products for Human Use
DCF	Discounted Cash Flow
DRG	NYSE Arca Pharmaceutical Index
EM(E)A	European Medicine Agency
FDA	Food and Drug Administration
HPR	Holding Period Return
IND	Investigational New Drug
IXIC	NASDAQ Composite Index
MPT	Modern Portfolio Theory
NASDAQ	National Association of Securities Dealers Automated Quotations
NBI	NASDAQ Biotechnology Index
NDA	New Drug Application
NME	New Molecular Entity
NYA	NYSE Composite Index
NYSE	New York Stock Exchange
OLS	Ordinary Least Squares
OTC	Over-The-Counter [Market]
PE	Price earnings ratio
R&D	Research and Development

SEC	Securities and Exchange Commission
US	United States
VaR	Value-at-Risk

LIST OF FIGURES

LIST OF TABLES

INTRODUCTION

Biotech and pharmaceutical companies (and many life science companies in general) research and manufacture products which are strictly regulated by regulatory governmental agencies. Announcements of such agencies to either approve or reject newly developed products are high-profile events which are of critical importance for the financial success of these products (Rothenstein, Tomlinson et al. 2011). As a consequence, these events are important valuation determinants of publicly traded companies and are closely monitored by investors (Herper and Langreth 2008).

Nowadays, investment professionals go to great lenghts in an effort to determine the most probable regulatory decision (approval or rejection) in advance and take trading positions accordingly. Many people, including investigators, company employees, outside consultants and agency staff are aware of results before they are made public. Too many a times have such professionals been paid by investment firms to provide 'expert opinions' which are in turn used by the investment firms to take trading positions (Steinbrook 2005). Use of such non-public information can indeed be very profitable as the information is not yet reflected in the market price of a stock and the price is expected to move in the desired direction. In anticipation of a positive decision by the regulatory agencies, an increase of the company's stock price is often observed which could be related to investors buying on this non-public news (Rothenstein, Tomlinson et al. 2011). In a way, this could be viewed as market efficiency as investors are absorbing information and valuing the company accordingly.

However, strong stock price movements of life science companies do not always reflect market efficiency. In 1998, the New York Times ran an article on a newly developed drug by EntreMed in its Sunday edition. The following Monday, the stock price of EntreMed more than quadruppled. But in fact, no new information had been presented as the drug was already reported in the scientific journal Nature and in various popular newspapers more than five months earlier (Huberman and Regev 2001).

In this thesis I will study the stock price reaction of companies listed on both the National Association of Securities Dealers Automated Quotations (NASDAQ) and the New York Stock Exchange (NYSE) to 403 positive and negative announcements made by the US Food and Drug Administration (FDA) and the European Medicine Agency (EMEA) between January 2008 and September 2012. Stock price movements prior to the announcement will be studied to investigate whether there is a systematic stock price anticipation and what its determinants could be. Furthermore, stock price movements on the announcement day will be studied to identify the determinants of a price shock. Lastly, the evolution of

stock prices in the days following the announcement will be studied to verify whether the response is efficient or possibly irrational as in the EntreMed case.

The remainder of this thesis is organised as follows. The first section gives a short introduction on the clinical trial and regulatory process encountered by life science companies developing new products. The second section studies how this development process can have an effect on the stock price of companies developing these products and gives an overview of existing literature on this topic. The third section gives an overview of the datasets and analysis framework used in this thesis. The fourth section studies stock price anticipation leading up to the announcement day using a methodology similar to the one used in a recent study on the stock price response to oncology drugs related FDA announcements (Rothenstein, Tomlinson et al. 2011). The fifth section deals with stock price responses on the announcement day itself using a company-specific return distribution approach. The sixth section deals primarily with stock price anticipation, response on the announcement day itself, and the potentially inefficient stock price behaviour following the announcement using an event-study framework (MacKinlay 1997; De Jong 2007). The seventh section proposes some trading strategies which can generate excess returns using the insights obtained in sections four through six. Simulations will show that excess returns can indeed be obtained using relatively low-risk strategies. The eighth and final section summarizes the main conclusions and gives an overview of possible future research.

1. CLINICAL TRIALS

1.1. THE SOFTENON CASE

Biotech and pharmaceutical companies (commonly known as life science companies) research, develop, and market products to cure or prevent diseases typically in humans[1]. However, as these products typically interfere with existing molecules in humans, effects of these newly developed products are sometimes unexpected and/or unpredictable and as a consequence bear high risks.

A classic example of such unexpected effects is the drug thalidomide (α-N-[phtalimido]glutarimide), having brand names such as Softenon, Contergan, Distaral, and others. Thalidomide was developed in the 1950s and eventually commercialised in 1957. At the time it was considered a 'wonder drug', able to cure many diseases and minor discomforts. The drug was initially designed as a sleeping pill, but was also used as a drug to cure headaches and colds, but more importantly to suppress morning sickness in pregnant women (Cohen 1960; Somers 1960; Franks, Macpherson et al. 2004). However, the drug was unknown to be teratogenic; women using thalidomide during the first trimester of the pregnancy gave birth to children with congenital malformations, i.e. missing or malformed limbs (phocomelia) (Giroud, Tuchmann-Duplessis et al. 1962; Speirs 1962).

Thalidomide is a racemic mix, consisting of very similar but different chemical molecules (R-thalidomide and S-thalidomide). In mice, S-thalidomide is responsible for the teratogenic effects; in rabbits both enantiomers are responsible for the effects. In humans, teratogenic effects are caused by only one of the two enantiomers. In principle, specific synthetisation of the non-teratogenic enantiomer should prevent enantiomer-related problems. However, researchers were not aware that S-thalidomide is converted into R-thalidomide (and vice versa) in humans, eventually making both enantiomers teratogenic in humans (Eriksson, Bjorkman et al. 1995; Matthews and McCoy 2003).

In the late 1950s and early 60s, more than 10,000 children in 46 countries were born with congenital deformities. Despite the known side effects, thalidomide was sold in pharmacies in Canada until 1962; Canada was the last country to end sales of the drug (Webb 1963). In the United Kingdom, the drug was approved in 1958 and withdrawn in 1961. Remarkably, it was never approved in the US (Bren 2001).

[1] Most of the large pharmaceutical companies such as Pfizer and Novartis for example have large animal health divisions developing pharmaceutical products specifically for non-humans. However, revenues are typically single digit percentages of the revenues obtained in the 'human health' division, are regulated to a lesser degree, and are generally of lesser importance. As a consequence, the animal health industry, albeit a growing industry, will not be studied in this thesis.

The effects of thalidomide increased the fear of the safety of medical drugs. The Softenon crisis was needed to implement the much needed change in the way regulatory institutions look at medical products. From then on, toxicology was assessed separately from pharmacology and efficacy by the regulatory agencies. Toxicology studies whether a product is safe to be used; pharmacology is typically divided into pharmacodynamics and pharmacokinetics; the former studies the effects of the drug on biological systems, the latter the effects of biological systems on the drug (absorption, distribution, metabolism, and excretion).

Currently, the main regulatory authorities going over drug approvals are the Food and Drug Administration (FDA) in the United States, Health Canada in Canada, the European Medicines Agency (EMEA) in Europe, and the Ministry of Health, Labour and Welfare in Japan.

1.2. COMMERCIAL RISKS IN DEVELOPING DRUGS

Life science companies bear incredible large risks regarding future revenues and related cash flows. Upfront investments are high, earn back periods are far away and short, and success depends on the competitive environment which is the result of the developments of competing companies.

1.2.1. UPFRONT INVESTMENTS

Upfront investments are frequently in the excess of $1 billion. In 1975, the life science industry spent the equivalent of $100 million in today's dollars for research and development (R&D) of an average drug approved by the FDA. By 2005, that figure had risen to $1.3 billion (Roy 2012). Different datasets and methodologies come to approximately the same conclusion. A study conducted by DiMasi and colleagues concluded that, currently, the average cost of an approved drug is $802 million (DiMasi, Hansen et al. 2003). Adams and Brantner recently concluded that the cost of an approved drug is on average $1 billion (Adams and Brantner 2010).

However, many products fail somewhere during the long research process and, as a consequence, are discontinued. When taking these lost investments into account and dividing the total amount of R&D investments by the number of approved drugs, the true cost of an approved drug is roughly $5 billion (Herper 2012). For example, between 1997 and 2011 Pfizer spent $108 billion on R&D and had 14 drugs approved by the FDA, resulting in an average cost per approved drug of $7.7 billion[2].

[2] Companies with a low success rate are off even worse. Between 1997 and 2011 AstraZeneca spent approximately $60 billion on R&D and had only 5 drugs approved by the FDA resulting in an average cost per approved drug of almost $12 billion. Novartis spent approximately $83 billion in the same period and had 21 drugs approved by the

Some are arguing excessive regulation and increased scrutiny by the FDA are 'killing' the life science industry (Herper 2012). Recently, the US House of Representatives investigated (Issa 2012) whether the strict FDA regulation is responsible for shortage of drug supplies in the USA[3]. The semiconductor industry, typically a research intensive industry, invests approximately $40,000 per year per employee on R&D. In the life science industry, that number has recently risen to over $100,000 per employee (Roy 2012). The costs are becoming so large that life science companies are becoming increasingly reluctant to invest in such risky endeavours.

1.2.2. PATENT PROTECTED PAYBACK PERIOD

In 1995, following the World Trade Organization's Agreement on Trade-Related Aspects of Intellectual Property Rights negotiated in the Uruguay Round, the patent term for medical drugs in the United States was changed from seventeen to twenty years from the earliest filing date (United States 2007). Although this might seem a lengthy period at first sight, sometimes this twenty years is still too short.

Life science companies file their drug candidates in the early stages of the R&D process. However, as this R&D process takes seven up to twelve years (Adams and Brantner 2010), the protected payback period of the investments is roughly ten years, meaning the invested money needs to be earned back in a relatively short period of time. Furthermore, many large pharmaceutical companies[4] are currently facing a 'patent cliff' where many of their top selling drugs are going off patent. Off patent drugs face stiff competition from generic competitors (Andrew 2012). Such drugs can see sizeable drops in sales even the first year the products go off patent[5], effectively making the patent protected period a relative hardcoded payback period (Danzon and Furukawa 2011; Pierson 2012).

FDA, resulting in an average cost of $4 billion per approved drug, demonstrating that even companies with high success rates face incredible steep upfront investment costs.

[3] The US House of Representatives report points out that between 2009 and 2011, the number of warning letters sent by the FDA to manufacturers (especially of generic injectable medications) almost quadrupled from 474 to 1720. Rather than pinpointing the precise problems with the drug manufacturing, the FDA has ordered costly general upgrades to plants, which lead to significant lapses in production. Four major producers of generic injectable drugs (Bedford Laboratories, Hospira Pharmaceuticals, Sandoz Pharmaceuticals, and Teva Pharmaceuticals) have reduced their combined production 30%, from 1 billion units per year to 700 million units per year.

[4] The top pharmaceutical companies are frequently considered to be a small group composed of Johnson & Johnson, Pfizer, Bayer HealthCare, GlaxoSmithKline, Roche, Sanofi, Novartis, AstraZeneca, Abbott Laboratories, Merck & Co., Bristol-Myers Squibb. and Eli Lilly. Also see Appendix 1.

[5] Sanofi and Bristol-Myers Squibb's blockbuster blood-thinner drug Plavix had sales of approximately €7 billion in 2011. The drug went off patent in May 2012 and third quarter (Q3 2012) sales dropped 96% to €50 million, evaporating billions of revenue.

As a consequence, life science companies want to speed up the R&D process as much as possible in an effort to maximize the protected payback period. In practice, these companies want to dispose of non-performing products as early as possible in the research process. After all, it makes no sense to keep adapting the product in a trial and error approach so that the total research period eventually exceeds the twenty year mark, rendering the patent protection void.

1.2.3. COMPETITIVE ENVIRONMENT

In general, the FDA and EMEA only allow new products to be commercialised when they perform better than the existing therapies or perform at least as good but with less side effects. However, as a company it is difficult to look ahead ten years and assess the products developed by the competitors. Company A might be developing a product which is better than the existing therapy, but so might company B. When company B's product reaches the market earlier then company A, company A's product might not be approved unless it performs even better than company B's product.

To avoid such risks, pharmaceutical companies tend to research and develop multiple potential drugs for a certain disease and discontinue many in the development process in the hope to have a single blockbuster product left in the end.

1.3. THE CLINICAL TRIAL PROCESS

To mitigate some of these aforementioned risks, a stepping stone (phased) approach is used in the development process. This approach allows a company to fairly cheaply dispose of non-performing drug candidates or drug candidates with unwanted side effects. Drug candidates passing an initial cheap screening undergo more thorough and expensive screenings until, hopefully, one of the many candidates passes all tests and is allowed to be commercialized.

Both the regulatory agencies (FDA and EMEA) and the life science companies have incentives to use a stepping stone approach. The regulatory agencies want to prevent a new Softenon case and companies want to make sure they have a product with a reasonable chance of success before starting lengthy and expensive clinical trials. Typically, the R&D process consists of a drug discovery process, a preclinical phase, clinical phases, and a registration phase (Meinert and Tonascia 1986; Cox Gad 2009). An overview of the process is shown in Figure 1.

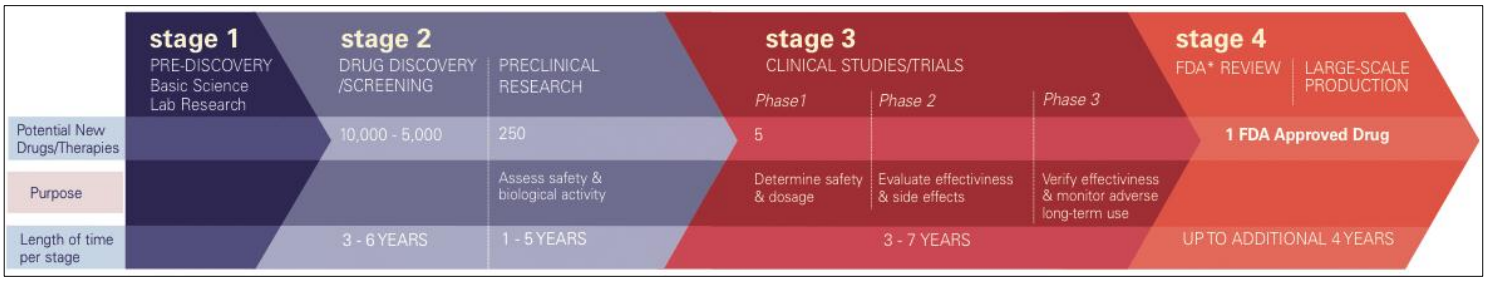

Figure 1: Overview of the drug discovery process. Source: FDA.gov

In the pre-discovery and drug discovery phase, a disease condition is thoroughly investigated. Using the insights obtained in the fundamental research, potential drug candidates are identified, optimized, and eventually pushed into the preclinical phase.

In the preclinical phase, experimental products undergo different tests, but not in humans; products may undergo pharmacodynamics, pharmacokinetics, and toxicity testing in animal models. The data obtained in this phase allows researchers to estimate a safe starting dose for testing in humans. After finalising these preclinical studies, products designed for the American market need an IND (Investigational New Drug) approval by the FDA to start further phases of the clinical trials.

In 2006, the FDA released a guidance document outlining recommendations for exploratory investigational studies. In these so-called phase 0 studies, conducted before traditional phase I trials, subtherapeutic doses of a new product are given to a small group of healthy volunteers (typically fewer than 15) for roughly a week to determine pharmacodynamic and pharmacokinetic properties. Researchers can then use these early data to guide further development (The Lancet 2009).

In phase I, similar to phase 0, researchers test an experimental drug or treatment in a small group of healthy people (<100) to evaluate its safety, determine a safe dosage range, and identify potential side effects. On average, phase I studies take a little more than 17 months and have a success rate of 75% (Adams and Brantner 2010).

In phase II, the experimental drug or treatment is given to a larger group of unhealthy people (100-300) to see if it is effective and to further evaluate its safety. This phase often consists of a phase IIa and phase IIb, where the treatment is given initially to a small group of unhealthy people (~20) to quickly assess effectiveness before initiating a larger and more expensive phase IIb study. On average, phase II studies take 31 months and have a success rate of 48% (Adams and Brantner 2010).

In phase III, the experimental drug or treatment is given to large groups of thousands of unhealthy people to confirm its effectiveness, monitor side effects, and compare it to commonly used treatments. On average, phase III studies take 27 months and have a success rate of 71% (Adams and Brantner 2010). After a successful phase III study, a product is typically filed for review at a regulatory agency (e.g. FDA or EMEA) for commercialisation. The company hands over the data obtained in the pivotal phases to the regulatory agency. The agency in turn analyses the data and then decides whether the company can commercialise the product or not. A successful phase III results almost always (~85%) in an approval of the product for commercialization.

To have a product approved by the FDA, a company needs to file an NDA (New Drug Application) and needs to demonstrate the new product is safe and effective when used as directed and that the benefits outweigh the risks. Furthermore, the company needs to demonstrate that it can adequately produce the product on a big scale and maintain quality, purity, and strength of the product (FDA 2013).

Phase IV studies consist of post-marketing studies to delineate additional information, including the treatment's risks, benefits, and optimal use. Phase III studies allow ‘only’ thousands of patients to be monitored compared to a phase IV study where the entire population of patients exposed to the specific drug are monitored. Occasionally products are withdrawn or use thereof restricted when phase IV studies for example indicate long term adverse effects or adverse effects for specific high-risk groups (Johnson-Pratt 2010).

2. INVESTING IN AN ENVIRONMENT OF REGULATORY UNCERTAINTY

2.1. VALUATING LIFE SCIENCE COMPANIES

Valuating a public life science company is difficult. Valuation methods typically include, amongst others, market capitalization over earnings (P/E ratio), market capitalization over sales, discounted future cash flow (DCF), and dividend growth models (Ross and Westerfield 2002). However, many pharmaceutical and biotech companies are 'one trick ponies' investing all available resources in a single product. This means a typical company has no approved products, hence no sales and most probably no profit. This renders many of these standard valuation methods unusable and many times an investor is left with a set of uncertain 'guesstimates' regarding the chance of approval, the size of the potential market, the pricing strategy of the company etc.

Inevitably, this uncertainty about future earnings leads to many differing opinions and different price targets amongst investors, and as a consequence, large price volatility (Rozelman 2011). However, one thing is certain: a lot of the approval uncertainty is taken away once the phase II hurdle is taken. A successful phase II study is a major value creating event as the experimental product has shown to be both safe (demonstrated in phase I) and to work (demonstrated in phase II).

Phase III trials are typically the most expensive part of clinical trials (Roy 2012). A negative phase III trial is often perceived as a very negative event for a life science company as it typically means a huge investment needs to be written down completely to zero. But even after a successful phase III study, uncertainty remains. The final decision to approve or refuse a product is made by the regulatory agency. On average, a small life science company, having a single product, who decides to file at the regulatory agency after a successful phase III clinical trial still has a 10-20% chance of having the filed product being rejected. So, an investor is often confronted with a discrete set of outcomes. There is either a big chance of an approval and subsequent earnings, albeit an uncertain amount, or a small chance of refusal and certainly no earnings.

Decisions by regulatory agencies can heavily affect stock prices of the product developing companies, especially when the company is relatively small. After all, the regulatory agencies decide whether the made investments are allowed to generate revenues or not. Recently, the FDA ruled negatively twice on 25 February 2013. Affymax' anemia drug Omontys was withdrawn under pressure by the FDA because patients complained about allergic reactions. The stock price plummeted 85% to $2.40. Dynavax

Technologies' Hepatitis B vaccine was refused by the FDA because Dynavax failed to effectively demonstrate the safe of the vaccine. The stock price was sent down 33% to $1.99 (Siddiqui 2013).

2.2. STOCK PRICE RESPONSES TO REGULATORY DECISIONS

2.2.1. STOCK PRICE ANTICIPATION

Knowledge of non-public clinical trial results or regulatory decisions before they are made public can offer a 'free lunch' opportunity for investors having access to this non-public information. However, when many people have access to this non-public information, a buying frenzy can affect the price of a drug company's stock in the runup to the actual announcement. Several scientific studies have tried to systematically investigate the role of insider trading in pharmaceutical and biotechnology companies.

Rothenstein and colleagues investigated the public announcements from 23 positive clinical trials, 41 positive FDA regulatory decisions ("winners"), 36 negative clinical trials, and 9 negative FDA regulatory decisions ("losers") between 2000 and 2009. All the trial results and regulatory decisions were regarding experimental anticancer drugs developed by the companies. The average stock price change from 60 days before the announcement to the actual announcement day was positive for the winners and negative for the losers. After the decision, the stock price increased on average for the winners and decreased for the losers (Rothenstein, Tomlinson et al. 2011). Overgaard and colleagues analysed the stock price anticipation of biotechnology stocks to 98 phase III trial decisions and 49 FDA regulatory decisions between 1990 and 1998. The average stock price change from 120 to 3 days before public announcement was significantly higher for the winners compared to the losers (Overgaard, van den Broek et al. 2000).

Both studies concluded that insider trading is the most likely explanation for the observed stock price anticipation prior to the announcement. Recently, researchers from academia have raised their concern about hedge funds and expert network firms which are constantly probing doctors, researchs and other academics for non-public information related to the clinical research (Ledford 2013). However, a recent study contradicts the idea that insider trading is responsible for the observed stock price anticipation. In his study, Goozner explains that it possibly is just a form of market efficiency: "The majority of the effect is probably unconscious. It's just leaking of information that eventually finds its way into the market place." He continues to explain that the observed decrease of the stock price of losers in anticipation of the decisions, especially for small companies, is just another form of market efficiency: "All of these micro-companies in phase III trials have been shopped to big companies. The ones that aren't sold are

the wallflowers, the leftovers. The good companies get bought, while the little companies doing phase III trials on their own are the ones probably headed for failure. [...] The success rate of 78% for large-cap companies, while the small-cap companies had no positive outcomes, was remarkable. The conclusion is to short these small-cap companies [...] when they have a drug in phase III clinical trials." (Goozner 2011).

It is Important to stress the difference between announcements of clinical trial results (e.g. phase III results) and announcements of regulatory agency decisions (e.g. FDA annoucements). Clinical trial results are much more prone to insider trading as there are more people involved and the chance of information leakage is always present. Furthermore, the day on which the non-public information will become public (i.e. the company announces the results) is much more uncertain, forcing an investor to act relatively fast to the non-public information. Decisions by the regulatory agencies on the other hand are taken relatively quick, mostly on a predetermined day, by a small group of people, seriously reducing the chance of information leakage. This is also demonstrated in the studies by Rothenstein and Overgaard. In both studies results were more outspoken in the case of the clinical trials, suggesting that insider trading happens more intensively using non-public clinical trial results than using regulatory decisions.

2.2.2. STOCK PRICE RESPONSE

Many researchers explored the effects of FDA drug authorizations on stock prices. A recent study using 344 FDA events revealed a significant wealth effect of 1.56% following a positive FDA announcement. This study also found that financial market losses from product development failures are much larger than financial market gains from product development successes; indicating an asymmetry in the response of financial markets (Sharma and Lacey 2004). A more recent event study demonstrated stock prices showing significant abnormal returns following a final FDA decision (Sarkar and de Jong 2006). A study conducted on a sample of life science companies from the United Kingdom also found positive stock price reactions to marketing authorization (Dedman, Lin et al. 2008).

Researchers tried to identify the cause of this observed stock price increase following approval by a regulatory body. The price reactions are not solely attributable to the positive information content but also reflect additional effects (Himmelmann and Schiereck 2012). As investors face many different investment alternatives, they primarily consider those that caught their attention. Increased media presence and a high level of attention affect buying behaviour and generate additional trading volume.

This attention-based stock demand in turn can push stock prices higher (Barber and Odean 2011). Other researchers concluded positive FDA announcements are accompanied by an increased trading liquidity which can result in higher stock prices (Himmelmann and Schiereck 2012). Liquidity effects are larger for smaller companies, so it would be reasonable to expect smaller companies to have larger stock price increases following a positive regulatory announcement (Lakonishok, Shleifer et al. 1992).

2.2.3. INSIDER TRADING SCANDALS

Recently, many insider trading cases related to the life science industry have surfaced. There are two reasons for this. Firstly, academic research is identifying new methods to detect potential insider trading cases (Berkman, Koch et al. 2012). Secondly, the Securities and Exchange Commission (SEC), the US federal agency responsible for enforcing the federal securities laws and regulating the securities industry, together with the Federal Bureau of Investigations (FBI), started investigating and prosecuting much more leads than in the past (Del Guercio, Odders-White et al. 2011). Of special interest are the so-called expert network firms which often employ prominent doctors and company executives as consultants. Several technology executives who consulted for expert network firms have already pleaded guilty to insider trading (Scannel 2012). Furthermore, the financial crisis has wiped out many investment companies and individuals, resulting in rogue behaviour in a desperate attempt to survive financially. Two examples demonstrate this hypothesis.

In April 2011, James Fan, a manager of clinical programming at Seattle Genetics, committed suicide in the parking of Newark Airport after the SEC discovered he had illegally tipped his brother about the results of a clinical trial at Seattle Genetics. He helped his brother gain $200,000, who needed the funds as he found himself deep under water after the real estate market collapsed in 2008 (Voreacos 2012).

In November 2012, the SEC alleged that $276 million in illegal profits or avoided losses were made by CR Intrinsic Investors by trading ahead of negative news in July 2008. The negative news included a clinical trial involving an Alzheimer's drug developed by Elan and Wyeth. A professor of neurology in an expert network firm at the University of Michigan Medical School tipped off a hedge fund run by CR Intrinsic Investors to liquidate $700 million in positions in Elan and Wyeth, as well as establish $960 million in short positions against the companies' shares (Goldstein 2012; Voreacos 2012)[6].

[6] This scandal was considered one of the most high profile insider trading cases of Wall Street as CR Intrinsic Investors is part of SAC Capital Advisors, a household name of Wall Street. At the end of 2008, the portfolio manager at CR Intrinsic Investors received a $9.3 million bonus, a significant portion of which was attributable to the drug-trial trades. The professor involved received more than $100,000 in expert network consulting fees.

2.3. RESEARCH FOCUS

Existing research almost exclusively focusses on stock responses of National Association of Securities Dealers Automated Quotations (NASDAQ) listed companies to clinical trial results or announcements made by the FDA. Research on stock responses of public companies listed on other exchanges such as the New York Stock Exchange (NYSE) or to announcements of other agencies such as the EMEA are very limited. I will try to fill this void by analyzing both NASDAQ and NYSE listed stocks in response to both FDA and EMEA announcements. I will extend my study to three periods: 1) the period preceding the actual announcement, 2) the days immediately following the announcements, and 3) the period following the actual announcement.

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3. DATASETS AND ANALYSIS FRAMEWORK

3.1. ANALYSIS TIMELINE

The exact dates of both the FDA and EMEA decisions are easy to be identified as there is no ambiguity in regards to the actual announcement date. The decisions made by the regulatory agencies are typically the result of a vote of a small panel of experts. Shortly after this vote, the decision is made public via either the FDA or the EMEA website.

However, the announcement can be made before a market opens or after a market closed. This problem is further complicated by the differences in time zones of 'overseas decisions'. For example, an FDA announcement at 2PM PST concerning a drug of a company listed on a European exchange has no immediate effect on the stock price of the European company because the European stock market is already closed. A solution to overcome this problem is to take a look at the cumulative return of day 0 (the actual day of the announcement) and day +1 (the first day post-announcement). In Figure 2, this would correspond with the window [T0, T3] and I will call this the 'announcement window'.

The period directly following the announcement window is the 'post-announcement window'. The period preceding the announcement window is the 'anticipation window'. The 'training window' is a long period preceding both the event window and the anticipation window, which is used to determine normal behaviour of the stock price. An overview is given in Figure 2.

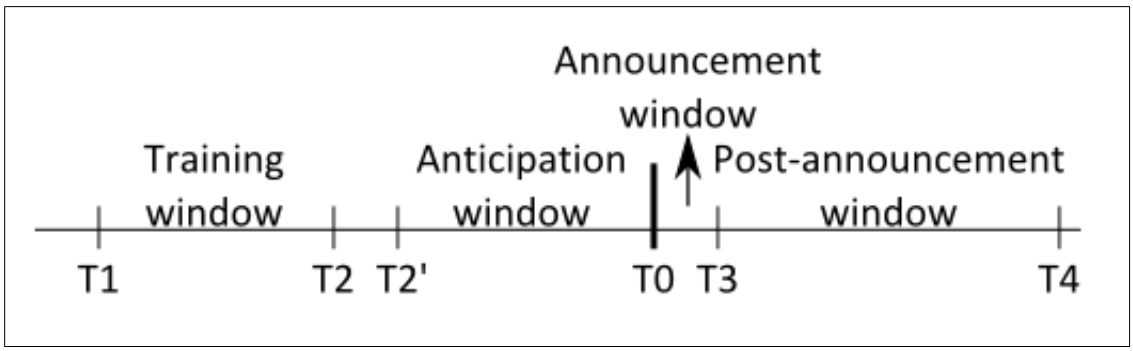

Figure 2: Overview of the timeline structure and different windows of an announcement event.

3.2. ANNOUNCEMENT EVENTS

Earlier studies by Overgaard and Rothenstein focussed on the periods 1990-1998 and 2000-2009. I will restrict my analyses to announcements made by the FDA and EMEA between January 2008 and September 2012.

3.2.1. FDA ANNOUNCEMENTS

The FDA is responsible for different types of product filings. The two most important filings are New Drug Application (NDA) filings and Biological License Application (BLA) filings. The NDA is a document submitted to the FDA to request approval to market a new drug. The BLA is a document submitted to the FDA to request approval to market a biologic. Moreover, the BLA is equivalent to an NDA for a biologic which can be a therapeutic DNA plasmid product, therapeutic synthetic peptide product of 40 or fewer amino acids, monoclonal antibody product for in vivo use, or therapeutic recombinant DNA-derived product (FDA 2013). In short, these filings correspond with the most innovative products and are of most importance for a company's earning potential and corresponding stock price. An overview of the BLA and NDA decisions are available from the FDA website[7]. For the period January 2008 – September 2012, 438 positive NDA and BLA decisions were recorded on the FDA website. Duplicate entries (e.g. simultaneous approval of different formulations or dosages) were removed from the data set.

Industry representatives caution that findings or data on refused products containing confidential company information could harm competition if made widely available (Heavey 2012). However, doctors and consumers could benefit from disclosure of the refused products. The FDA is looking into ways the agency can make its regulatory decisions more transparent and systematically report both approvals and refusals. At the moment, however, products refused by the FDA are not officially publicly disclosed by the FDA nor systematically listed on the FDA website. Nevertheless, companies typically disclose it publicly when they receive a Complete Response Letter (CRL) from the FDA indicating a certain product was refused. An internet search using keywords such as 'CRL overview', 'FDA refusal overview', and 'refused FDA drugs' yielded 69 negative FDA announcement events[8].

3.2.2. EMEA ANNOUNCEMENTS

Similar to the FDA, the EMEA lists several different types of approvals on a public website. Unlike the FDA, however, the EMEA lists approved, refused, suspended, and withdrawn products. Products for human use (EMEA/H/C designation) are new drugs designed for human consumption and are the products of importance in this study. A list of approval and refusal events was obtained from the EMEA

[7] A list of all the FDA approved products (NDA and BLA) can be downloaded per month from the following URL: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Reports.NewOriginalNDA.

[8] Several websites list specific overviews of drugs refused by the FDA. Two excellent overview websites are the Vaughns website and the RTTnews website, available from respectively: http://www.vaughns-1-pagers.com/medicine/prescription-drugs-rejected.htm and http://www.rttnews.com/CorpInfo/FDACalendar.aspx.

website[9] as described in earlier studies (Downing, Aminawung et al. 2012). In total, 326 positive and 12 negative EMEA announcements were recorded between January 2008 and September 2012. Similar to the FDA announcements, duplicate entries were removed from the data set.

3.2.3. LINKING ANNOUNCEMENTS TO STOCK TICKERS

Each of the FDA and EMEA announcements was linked to a publicly traded company if possible; private companies were discarded from the dataset. When a company is listed on multiple exchanges (e.g. Novartis is traded both on the Swiss exchange and on NYSE as `SIX:NOVN` and `NYSE:NVS` respectively), the American ticker was taken.

3.2.4. SAMPLE SELECTION

Of the 438 positive FDA announcements, 130 could be associated with a private company. Consequently, these 'private announcements' were removed from the dataset. If a company had two different drugs with positive or negative announcements close to each other, only the earlier announcement was retained in the dataset.

Regulatory decisions on products developed by companies which entered the market through an initial public offering (IPO) close to the actual announcement day were removed from the dataset. Companies often use the attention and momentum of a positive FDA or EMEA announcement to raise capital through an IPO. This was of special importance in the aftermath of the recent financial crisis where investor sentiment was low and the number of IPOs per year was at a record low[10]. A company trying to have an IPO could use any good news or momentum to open up the IPO window (Gaoa, Ritterb et al. 2012). However, despite the frequent positive FDA decisions, many of the recent biotech IPOs were no great successes as companies frequently had to slash their IPO price forks or lower the amount of shares to be floated[11].

These IPO related announcements were excluded from the dataset as there is frequently large stock price volatility attributable to the IPO event, rather than the announcement event. Data availability

[9] http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp

[10] Between 1988 and 2011, there were on average 32.5 IPOs per year on the NASDAQ, NYSE, and Amex exchanges combined. In 2008, there were only 7 IPOs, in 2009 there were 12, in 2010 45, and in 2011 22.

[11] Supernus Pharmaceuticals planned to sell 5.8 million shares and hoped to fetch as much as $12 or $14 a piece. After being postponed more than sixe months, 10 million shares were sold at $5 a share in the beginning of January 2012. At the end of Novermber 2010, Zogenix raised a total of $56 million by offering 14 million shares at $4 a share. However, The company initially planned to raise close to $90 million by offering 6 million shares at $12 and $14 a share. In August 2010, Trius Therapeutics offered 10 millions shares at $5 a share, after initially planning to sell six million shares at a price range between $12 and $14 a share.

problems also occur as there is no training window or anticipation window data available as the shares were not yet floating at that time.

Companies which were subject of a takeover or merger during the January 2008 – September 2012 period were also removed from the dataset as these stocks also suffer from large stock price volatility and problems with data availability once the merger is finalised.

After cleansing the dataset, approximately 70% of the positive FDA announcements can be linked to a publicly traded company. Approximately 50% and 20% of these public companies is listed on the NYSE and NASDAQ respectively (see Appendix 4 for more detailed information). Numbers are fairly similar for EMEA announcements (Appendix 5). As the largest portion of the announcement events can be linked to NYSE and NASDAQ listed companies, this thesis will exclusively focus on the stock price responses of companies listed on these two exchanges. In total, 403 events are studied of which a breakdown per exchange and agency is given in Table 1.

Table 1: Overview of the announcement events between January 2008 and September 2012 per agency and exchange.

	FDA			EMEA			Total
	Positive	**Negative**	**Total**	**Positive**	**Negative**	**Total**	
NASDAQ	48	43	91	16	3	19	110
NYSE	140	8	148	142	3	145	293
Total	188	51	239	158	6	164	403

Of the 403 announcements made between January 2008 and September 2012, 346 were positive and 49 negative. Remarkable differences appear when the announcements are separated per agency and per exchange on which the companies are publicly listed (Table 1). Forty-eight FDA announcements on drugs of NASDAQ listed companies were positive compared to 43 negative announcements. However, FDA announcements on drugs of NYSE listed companies were allmost exclusively positive. Both the number of positive and negative EMEA announcements of drugs developed by NASDAQ listed companies is lower than is the case with FDA announcements. The FDA and EMEA announcements of drugs developed by NYSE listed companies are similar.

Several possible explanations exist for this observed difference between NASDAQ and NYSE listed drug developers. First, I manually aggregated the negative FDA announcements from different websites which mainly focus on companies developing innovative (and hence controversial) therapies with a potential significant impact on the stock price; such (small) companies are typically listed on NASDAQ. Second, the market capitalization of companies with approved products is typically larger than the

market capitalization of companies with failed drug candidates. Larger (pharmaceutical) companies typically list on NYSE, rather than on NASDAQ (Goozner 2011). Third, closely related to the previous point made, big (pharmaceutical) companies have had many successes in the past and have more experience in properly designing and carrying out clinical trials and filing for approval at the regulatory agencies. As a result, the success rate increases with company size and repeated approval of other drugs (Sarkar and de Jong 2006). Fourth, a large company like Pfizer or Novartis might easily discontinue promising project in the later stages of clinical trials, even if this means a significant loss of invested money. Indeed, the big pharmaceutical companies have many approved cash flow generating products in the market providing sufficient buffers to overcome occasional setbacks. Small NASDAQ companies, however, typically are developing one or a few products and are cash flow negative. These companies might be forced to file not-so-promising drugs for approval in a desperate attempt as the only alternative is to discontinue their only potential source of future income. Fifth, NASDAQ listed companies typically develop more experimental or more innovative products which have a bigger chance of failure as the FDA typically does not have a standard 'roadmap' for such products[12].

The observed difference between the FDA and EMEA is a little more difficult to explain. However, there are some intuitively plausible explanations. First, NASDAQ listed companies are typically smaller than NYSE listed companies and as a consequence will focus on their US home market rather than on Europe, hence the smaller amount of 'NASDAQ announcements' by the EMEA. It is not uncommon for a small US based company to file a product locally at the FDA and license out the rights abroad to another company, frequently a large pharmaceutical company with an established (global) distribution network. Second, the NASDAQ is typically faster than the EMEA to approve products (FDA 2010), hence a US based company will normally first file at the FDA to have a quick answer and then proceed to file at the EMEA if the filing was successful. Third, large pharmaceutical companies with headquarters outside the US are typically listed on multiple exchanges, including the NYSE. These large companies can successfully file products simultaneously at both the FDA and EMEA. Hence, 'NYSE announcements' are almost identical for the FDA and EMA.

[12] ChondroCelect, developed by the Belgian company Tigenix, is the first cell-based product to be approved by the EMEA as an Advanced Medicinal Therapy. Rather than being a standard drug, cells are removed from a patient's knee, treated, and reinjected into the knee. The treated cells than cure the cartilage damage inside the patient's knee. As this type of therapy was completely new, no standard FDA roadmap existed, and although the product was already approved by the EMEA and is commercially available in Europe, the product was refused by the FDA.

Throughout this thesis I will refer to companies listed on the NASDAQ which have products approved by the FDA as 'FDA positive NASDAQ Assets', companies listed on the NYSE which have products refused by the EMEA as 'EMEA negative NYSE Assets' etc.

3.3. STOCK PRICE DATA AND INDEX DATA

3.3.1. STOCK PRICE DATA

Daily stock price information for all the NYSE and NASDAQ Assets was retrieved from the Finance Yahoo website using an automated retrieval strategy[13]. Through a combination of existing software packages and a set of custom made packages, the stock price information was stored in a local relational MySQL database, optimized for the analyses described in this thesis.

3.3.2. INDEX DATA

In many analyses, daily stock returns need to be compared to a reference index or analysed using the return on a reference index. For both the NYSE and the NASDAQ, a broad index and smaller life science related index were selected (Table 2). Daily values of these indexes was retrieved using a strategy similar to the one explained above.

Table 2: Overview of the used reference indexes.

Index name	Ticker	Exchange	Index type
NYSE Composite (DJ) Index	^NYA	NYSE	Broad
NYSE ARCA Pharmaceutical Index	^DRG	NYSE	Small / life science
NASDAQ Composite Index	^IXIC	NASDAQ	Broad
NASDAQ Biotechnology Index	^NBI	NASDAQ	Small / life science

3.4. DATA ANALYSIS FRAMEWORK

A large quantity of data needed to be analysed and aggregated, and this for different agencies (FDA and EMEA), different exchanges (NASDAQ and NYSE), and different announcements (positive and negative). To ensure an identical analysis methodology over all different datasets, avoid human errors, speed up analyses, and automate analyses in general, an analysis framework was developed in Perl and R which allows each of these goals to be met. A more detailed overview of the analysis framework is given in Appendix 6.

[13] Stock price information can manually be downloaded for each stock from the Finance Yahoo website: http://finance.yahoo.com. However, there are automated strategies available which can automate data retrieval. A good example is the `Finance::QuoteHist` Perl package which makes use of the Finance Yahoo CSV API, explained in detail at https://code.google.com/p/yahoo-finance-managed/wiki/csvHistQuotesDownload.

4. STOCK PRICE ANTICIPATION – AVERAGED CUMULATIVE RETURNS

Earlier research indicated insider trading might be a frequent phenomenon in the life science industry. This is often demonstrated by stock price appreciation prior to positive news and stock price depreciation prior to negative news regarding clinical trials or regulatory announcements. This section investigates stock price behaviour of NYSE and NASDAQ listed companies prior to FDA and EMEA announcements.

4.1. METHODOLOGY

4.1.1. MEAN AND VARIANCE OF CUMULATIVE RETURNS

Day 0 is the day the final FDA or EMEA decision is announced. The stock price of the companies which developed the products being approved or refused were recorded for each of the 60 consecutive trading days before day 0, day 0 itself, and the 15 consecutive trading days following day 0. This corresponds with approximately four calendar months excluding weekends and holidays. This strategy is similar to the one applied in a number of earlier studies on insider trading and/or stock price anticipation (Rothenstein, Tomlinson et al. 2011).

The rate of return for an individual stock i was calculated as a buy and hold holding period return (HPR) assuming the stock was purchased at day -61 using the following formula:

$$R_{i,j} = \frac{P_{i,j} - P_{i,-61}}{P_{i,j}} \tag{1}$$

where $P_{i,-61}$ is the closing price of stock i at day -61 and $P_{i,j}$ the closing price of stock i at day j. Using this formula, the real cumulative return on each trading day was calculated assuming the stock was purchased at day -61. Assuming there are z announcement events and consequently z stock price evolutions to be analysed, the cumulative returns can be represented using the following matrix notation:

$$\begin{bmatrix} R_{a,-60} & R_{a,-59} & \dots & R_{a,1} & \dots & R_{a,15} \\ R_{b,-60} & R_{b,-59} & \dots & R_{b,1} & \dots & R_{b,15} \\ \vdots & \vdots & \ddots & \vdots & \ddots & \vdots \\ R_{z,-60} & R_{z,-59} & \dots & R_{z,1} & \dots & R_{z,15} \end{bmatrix}. \tag{2}$$

The average stock price evolution of the entire set of announcement events can be approximated by calculating averaged cumulative returns, which are obtained by averaging over each column in the matrix in equation (2) using the following formula:

$$\bar{R}_J = \frac{1}{z} * \sum_{i=a}^{z} R_{a,j} \quad (3)$$

where $\bar{R}_J$ represents the average cumulative return at day j; eventually resulting in a single series of average cumulative returns:

$$[\bar{R}_{-60} \quad \bar{R}_{-59} \quad \dots \quad \bar{R}_1 \quad \dots \quad \bar{R}_{15}]. \quad (4)$$

The returns of NASDAQ and NYSE listed stocks were compared to returns (calculated in a similar fashion) of appropriate indices. Returns of NASDAQ Assets were compared to returns of both the NASDAQ Biotechnology Index (^NBI) and the NASDAQ Composite Index (^IXIC). Returns of NYSE Assets were compared to the NYSE Composite Index (^NYA) and the NYSE Pharmaceutical Index (^DRG).

Similarly, the variance for each trading day can be calculated over each of the announcement events. This can be represented by calculating the sample variance over each column of the matrix in equation (2) using the following formula:

$$\sigma^2_{\bar{R}_j} = \frac{1}{z-1} * \sum_{i=a}^{z} \left(R_{a,j} - \bar{R}_J\right)^2 \quad (5)$$

where $\sigma^2_{\bar{R}_j}$ represents the variance of the cumulative returns at day j calculated over z announcement events.

4.1.2. TESTING DIFFERENCES FOR SIGNIFICANCE

The research question is whether the average cumulative return of the FDA positive NASDAQ Assets at a specific day is larger than the average cumulative return of a specific reference index. This can be statistically tested using a standard t-test. However, the standard t-test comes with a series of conditions which need to be met before it can be applied. The most important conditions are the equality of variances of the compared samples and normality of the data.

However, the standard t-test is not valid in case any of the aforementioned two conditions are not met. Equality of variances can be tested using Bartlett's test (Bartlett 1937). Furthermore, it is known that daily stock returns, especially daily NASDAQ returns, are not normally distributed (Brown and Warner 1985; De Jong 2007). This is also clearly demonstrated in Appendix 7. Even in case the variances would be identical, the non-parametric Wilcoxon rank-sum test (also known as the Mann–Whitney U test) is a much safer method to test equality of the cumulative means (Wilcoxon 1945).

4.2. RESULTS AND DISCUSSION

4.2.1. FDA - NASDAQ

The average cumulative returns for each trading day were calculated separately for positive and negative FDA and EMEA announcements and separately for NASDAQ and NYSE Assets. Further sections will also have these different subsections.

The average cumulative return at day -1 for the FDA positive NASDAQ Assets is 23.76%, compared to 7.63% and 3.76% for the ^NBI and ^IXIC respectively (Table 3). The variances of the cumulative returns at day -1 are 29.87%, 0.99%, and 1.13% for the NASDAQ Assets, ^IXIC and ^NBI respectively. The variance at day -1 of the NASDAQ Assets differs from both the ^NBI ($p < 0.0001$) and the ^IXIC ($p < 0.0001$). The variance of both indexes does not differ ($p = 0.64$). Variances also differ in the FDA – NYSE, EMEA – NASDAQ, and EMEA – NYSE case (data not shown). Clearly, using the Wilcoxon rank-sum test is the safer method to test for equality of the means and consequently this test will be used throughout this section.

The return of the FDA positive NASDAQ Assets at day -1 is significantly higher than the returns of the ^NBI ($p = 0.0004$) and the ^IXIC ($p < 0.0001$). One explanation for this observation could be that the stocks under consideration systematically outperform the reference indexes, independently of the announcement events. To test whether this positive and significant anticipation is indeed announcement event-driven, NASDAQ Asset returns were compared to the performance of a random index generated using the same NASDAQ listed companies but random dates. The returns at day -1 are significantly larger for the NASDAQ Assets compared to this random index ($p = 0.0291$), from which can be concluded the observed stock price anticipation is indeed announcement event-driven.

Next to the positive anticipation, there is a clear positive response the day following a positive FDA announcement; the average cumulative return goes from 23.76% on day -1 to 39.91% on day +1. At first sight, there appears to be an initial overshoot as the cumulative return at day +15 is slightly lower than the cumulative return at day +1 (Figure 3). However, it is difficult to statistically test these observations in this framework and these observations will be tested in further sections.

The average cumulative return at day -1 for FDA negative NASDAQ Assets is 24.22%, compared to 7.51% and 6.20% for the ^NBI and ^IXIC respectively (Table 3). The cumulative return at day -1 is higher than the return of both the ^NBI ($p = 0.0002$), the ^IXIC ($p = 0.0003$), and a random index generated in a similar fashion as described before ($p = 0.0004$).

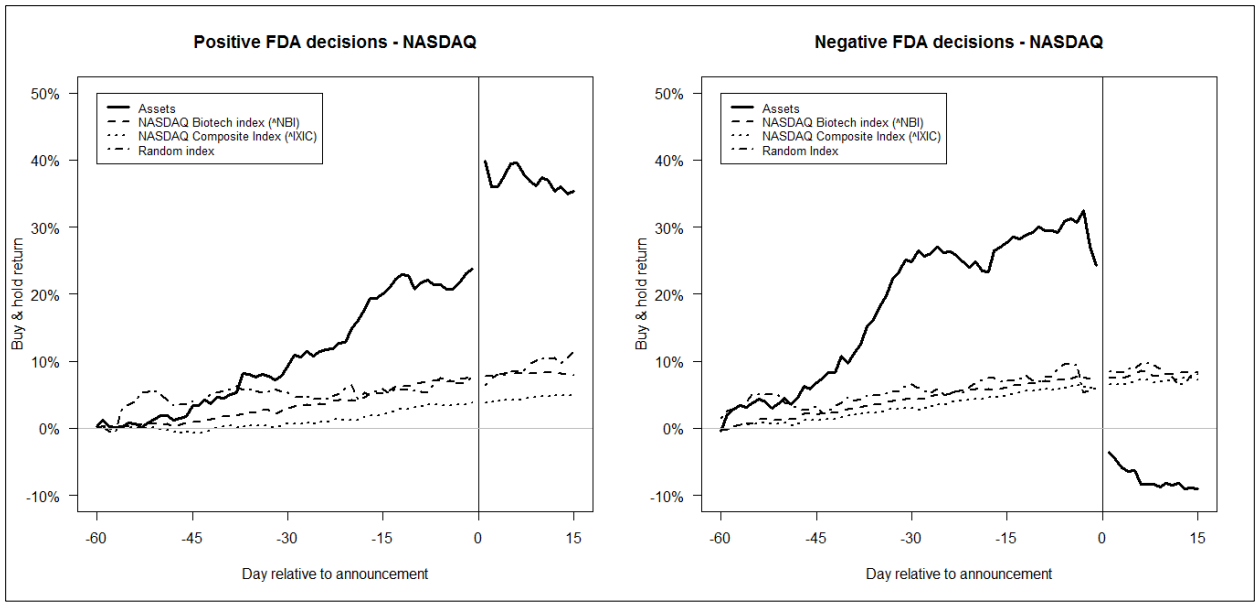

Figure 3: Overview of the evolution of the cumulative HPR of drug developing companies and appropriate indexes listed on the NASDAQ starting at day -60 relative to positive and negative FDA announcements.

There is a negative response the day following a negative FDA announcement; the cumulative return drops from 24.22% on day -1 to -3.64% on day +1, evaporating all gains obtained in the anticipation window. Also, there appears to be an initial undershooting as the cumulative return at day +15 is lower than the cumulative return at day +1 (Figure 3). But again, these observations need to be statistically tested in further sections. Furthermore, it is striking the decline appears to be starting approximately around day -5 which could indicate a sharp sell-off of certain market participants anticipating negative news, possibly having non-public information. However, another explanation is that the some of the announcement dates are inaccurate (as they were obtained using an internet search) and a portion of the large decline following the negative announcement would be captured in the anticipation window. Regardless of the FDA refusal data quality, it is clear there is no large negative anticipation starting a long period before the actual negative FDA announcement, as suggested by other researchers (Rothenstein, Tomlinson et al. 2011).

Furthermore, these observations are quite surprising at first sight as this means the market is inefficient. Market participants are bad at guessing the outcome of an FDA decision, despite the large amount of (clinical) data publicly available. The market is just assuming FDA decisions have positive outcomes per definition and push the prices higher in anticipation of the actual announcement. Other researchers, however, have indicated stock prices can also increase when investors are becoming aware of the existence of certain companies (Barber and Odean 2011). Following this reasoning, investors unfamiliar

with a particular life science company might become informed about the company as the media is frequently indicating important FDA decisions are due. This awareness might cause an additional stock demand and push stock prices higher.

The cumulative return at day -1 is similar for both the positive and negative FDA announcements; the returns do not differ statistically (p-value = 0.555). This also means insider trading does not appear to be a significant problem in regards to FDA decisions, whereas it can be (and probably is) a larger problem in regards to the results of phase II/III clinical trials (Rothenstein, Tomlinson et al. 2011). This makes sense once one realizes the FDA decision is a ruling based on the voting of a small and independent panel compared to clinical trials which is a lengthy process involving many persons.

At first sight, this market inefficiency offers a 'free lunch' opportunity by going 'long' at day -60, closing the position close to the announcement date, going 'short' at day +1 and closing the position at for example day +15. The results of such, apparently risk-free, trading strategies will be investigated into more detail in further sections.

Table 3: Average cumulative HPR at day -1, +1, and +15 assuming the stock was bought at day -61.

	FDA						EMEA					
	positive			negative			positive			negative		
	-1	+1	+15	-1	+1	+15	-1	+1	+15	-1	+1	+15
NASDAQ	23.76	39.91	35.37	24.22	-3.64	-8.99	14.69	13.87	19.27	5.87	4.59	10.48
^NBI	7.63*	7.79	7.91	7.51*	7.63	8.83	2.07	2.36	2.07	2.73	2.52	7.32
^IXIC	3.76*	3.79	4.97	6.20*	6.52	7.27	-0.09	-0.17	0.17	8.38	6.32	7.26
NYSE	1.75	2.03	2.96	-0.57	-0.18	-0.25	2.88*	2.73	2.02	-2.44	-1.64	-3.33
^DRG	0.92*	0.88	1.29	-0.30	-0.87	-1.06	1.66	1.43	1.61	-1.85	-2.77	-2.02
^NYA	0.14*	0.49	0.66	2.44	1.88	1.33	0.13	-0.33	0.14	-10.82	-11.10	-7.92

NASDAQ indicates the averages of the 'NASDAQ Assets', NYSE indicates the averages of the 'NYSE Assets'. All numbers are percentages.

* Indicates the average cumulative return of the Index differs significantly from the average cumulative return of the Assets (Wilcoxon rank-sum test, 5%); only tested at day -1.

4.2.2. FDA - NYSE

The average cumulative return at day -1 for the FDA positive NYSE Assets is 1.75%, compared to 0.92% and 0.14% for the ^DRG and ^NYA respectively (Table 3). Although the average cumulative return of the NYSE Assets at day -1 is only slightly higher than the return of both indexes, the return is statistically higher than the return of the ^DRG (p = 0.0059) and the ^NYA (p = 0.0099).

There appears to be only a slight response to the actual announcement as the cumulative return of the Assets at day +1 only increased to 2.03%, slightly higher than the cumulative return at day -1 (Figure 4). Again, this will be evaluated into more detail in further sections.

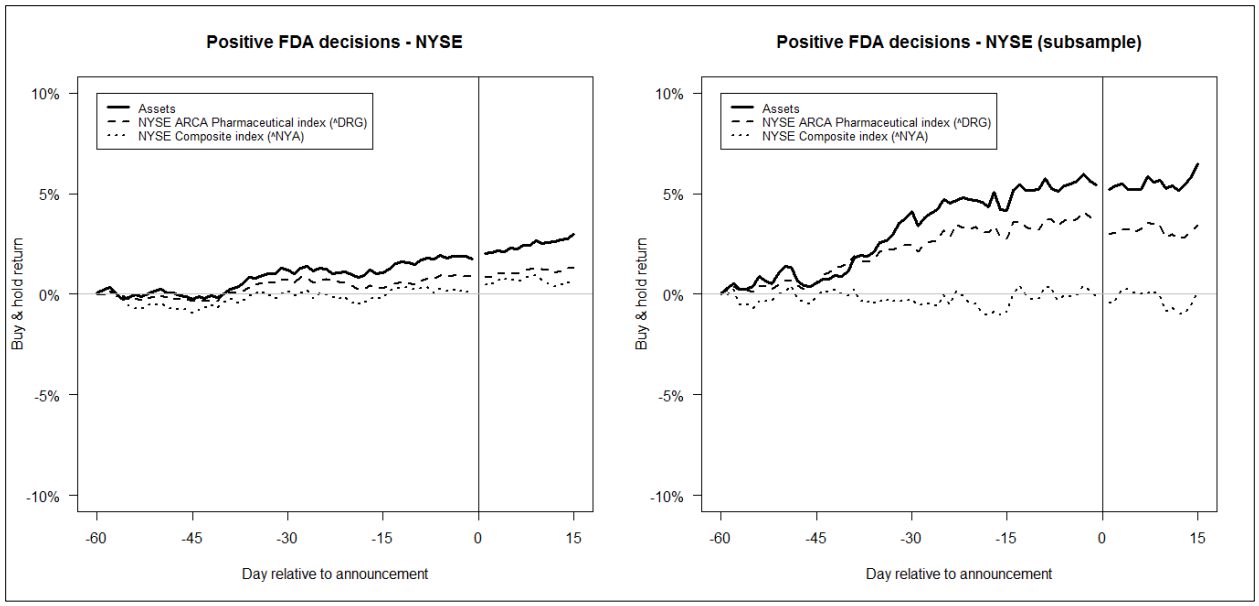

Figure 4: Overview of the evolution of the cumulative HPR of drug developing companies and appropriate indexes listed on the NYSE starting at day -60 relative to positive FDA announcements. The subsample refers to the products which are NDA type '1' and review classification 'Standard'.

Different explanations can be proposed for the observed difference between the FDA positive NASDAQ and NYSE Assets. First, NYSE listed companies are larger and frequently have a large number of products already in the market. Individual positive (or negative) announcements have small effects on the total revenue and profits of a company. Second, many of the NYSE listed companies included in the dataset produce low profit products or therapies such as medical devices (e.g. baxters), food additives (e.g. vitamins), and generic drugs which have a relative small market potential.

In an effort to eliminate these 'low profit FDA announcements' from the dataset, a subsampling was carried out. This subsample only contained completely new drugs (NDA type '1') which followed the standard procedure (review classification 'S')[14]. In total, 23 such announcements were present in the sample. The average cumulative return at day -1 is larger than return obtained using the full dataset (Figure 4). The average cumulative return of the NYSE Assets at day -1 is significantly larger (despite the lower sample size and power) than the cumulative return of ^NYA ($p = 0.0275$). However, the return of the Assets is not statistically larger than the return of the ^DRG ($p = 0.0756$). This is not surprising as the

[14] The FDA categorizes new drug applications (NDA) on a 1 to 6 scale according to the novely. For example, a '1' is an application for a completely new molecular entity (NME), a '5' is an application for a new manufacturer willing to produce an already approved product and a '6' is an application to use an already approved drug in a new indication. Review classification is either standard review ('S') or priority review ('P'). A detailed overview of the classifications is available at http://tiny.cc/wzxttw.

^DRG is an index composed of 16 large pharmaceutical companies (see Appendix 8) which are mostly the companies present in this specific subsample.

The average cumulative return at day -1 for the FDA negative NYSE Assets is -0.57%, compared to -0.30% and 2.44% for the ^DRG and ^NYA respectively. As the sample size is relatively small, the non-parametric statistical testing does not yield any significant results. The return at day -1 is not statistically larger than the return of both the ^DRG and the ^NYA (p-values are both 1.00), nor does it statistically differ from the anticipation observed in the FDA positive NYSE Assets (p = 0.7121).

4.2.3. EMEA – NASDAQ

The average cumulative return at day -1 for the EMEA positive NASDAQ Assets is 14.69% compared to 2.07% and -0.09% for the ^NBI and ^IXIC respectively (Table 3). However, the return is not significantly larger than the return of both the ^NBI (p = 0.1908) and ^IXIC (p = 0.0705). This is largely due to the low number of observations (n=16) included in the analysis making the statistical testing not robust enough. The cumulative response of the NASDAQ Assets at day -1 is also not statistically larger than the return of the random generated index (p = 0.3478).

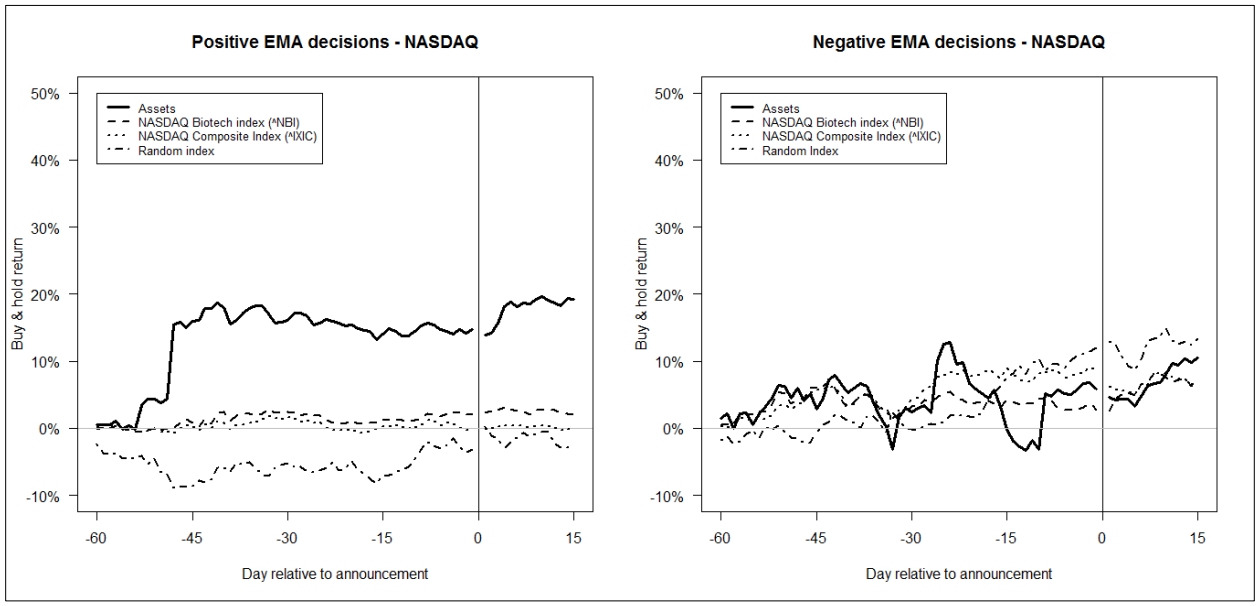

Figure 5: Overview of the evolution of the cumulative HPR of drug developing companies and appropriate indexes listed on the NASDAQ starting at day -60 relative to positive and negative EMEA announcements.

The response on the day following the public announcement is much smaller than the response observed for the NASDAQ Assets in response to FDA announcements. Furthermore, the largest portion of this assumed anticipation is caused by an event happening around day -50 (Figure 5). This can be explained by the structure of the reviewing process applied by the EMEA. Prior to the final decision, the

EMEA Committee for Medicinal Products for Human Use (CHMP) decides on a non-binding opinion[15] and makes this opinion public. The EMEA then issues a final decision approximately two months later. The -50 day (trading days) coincides with this period wherein the CHMP issues the opinion. Apparently, market participants process the opinion issued by the CHMP as it were a final decision and treat the final decision made by the EMEA as a non-event.

The response of NASDAQ assets on negative EMEA decisions is difficult to assess as there were only three assets available and no clear pattern emerges from the data, as can be seen in Figure 5. Consequently, this dataset will also not be analysed in furhter sections either.

4.2.4. EMEA - NYSE

The average cumulative return at day -1 for the EMEA positive NYSE Assets is 2.88% compared to 1.66% and 0.13% for the ^NBI and ^IXIC respectively (Table 3). This return is significantly larger than the return of the ^DRG ($p = 0.0019$), but not significantly larger than the return of the ^IXIC ($p = 0.1404$). Results for the subsample (identical to the subsampling strategy carried out for the FDA positive NYSE Asssets) are very similar to the results obtained in using the full dataset (Figure 6).

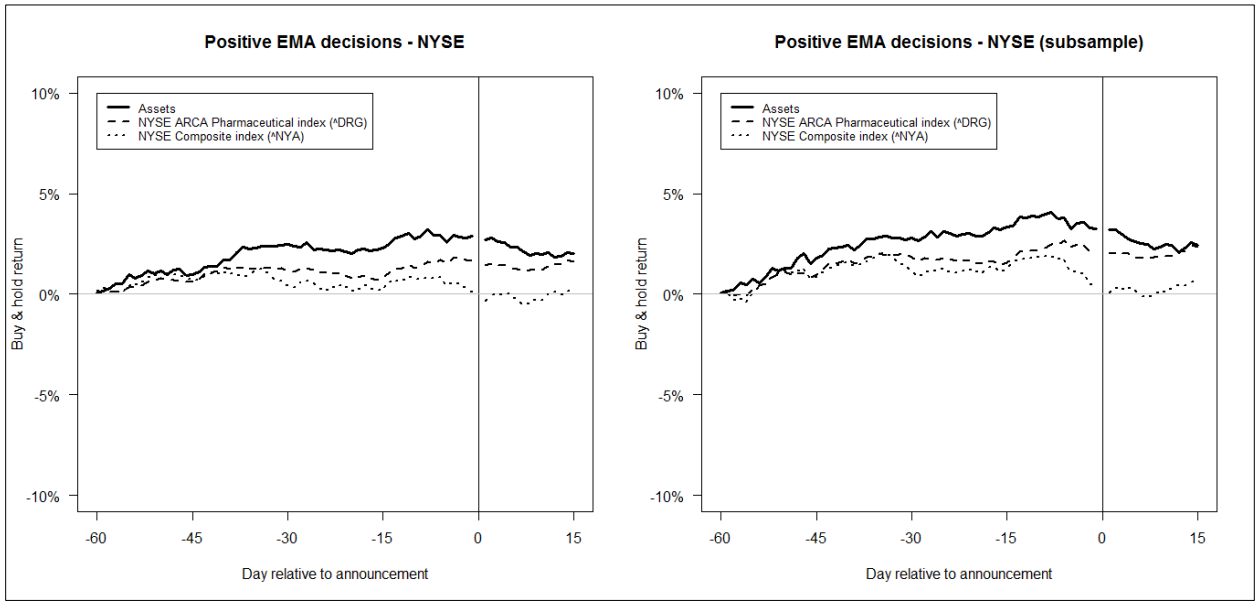

Figure 6: Overview of the evolution of the cumulative HPR of drug developing companies and appropriate indexes listed on the NYSE starting at day -60 relative to positive EMEA announcements. The subsample refers to the products which are NDA type '1' and review classification 'Standard'.

[15] The CHMP Opinion is issued by the EMEA and is a non-final and non-binding opinion based on the submitted application file as it is. Companies can append or modify the application file in case the opinion would be negative. 67 days later, based on the appended or modified file, the CHMP issues a Final Commission Decision. A positive opinion is typically followed by a positive final decision.

The relatively clear spike at about day -50 observed in Figure 5 is not present in the case of EMEA positive NYSE announcements. The response on the day following the public announcement is also much smaller than the response observed for the NASDAQ Assets in response to the FDA announcements. The response of NYSE Assets to negative EMEA decisions is difficult to assess as only three announcements are available and no clear pattern emerges from the data (data not shown).

4.3. CONCLUDING REMARKS

Over a 60 trading days window prior to an FDA or EMEA announcement, NASDAQ listed companies outperform both a broad market index and a more specific life science index. NYSE listed companies outperform a broad market index and a more specific life science index in case of positive FDA announcements. Both NYSE and NASDAQ listed companies do not systematically outperform different reference indexes in anticipation of EMEA announcements.

There is no clear evidence of frequent and widespread insider trading occuring in anticipation of FDA or EMEA announcements. However, in some cases stock prices depreciate prior to negative FDA announcements, only partially offsetting the anticipation increases gained. There is no long-term underperformance prior to negative annoucements.

There are some problems with the strategy described in this section. First of all, this strategy does not allow stock price responses on the announcement day or the period following the announcement day to be analysed without recalculating all individual holding period returns. Furthermore, this strategy does not correct for global market movements or different exposures of companies to market movements ('beta'). For example, imagine a situation where one company experiences a stock price increase of 50 % and 10 stocks a stock price decrease of 1%. Now also assume the former company has a volatility of 50% and the latter companies a volatility of 0.5%. Clearly the 1% stock price decreases are more important than the 50% increase of the more volatile company. However, this would not be obvious using the strategy outlined in this section. These problems will be addressed in a further section using the event study methodology.

5. ANNOUNCEMENT DAY EFFECT – DISTRIBUTIONAL ANALYSIS

The previous section focussed largely on stock price appreciation in the period leading up to the actual announcement event. Before addressing the problems outlined in the previous section using an event study framework, this section will investigate how exceptional stock price movements are in the announcement event window. This will be investigated by identifying the average position of the daily announcement event window return in a distribution of historical daily returns.

5.1. METHODOLOGY

5.1.1. OBTAINING DISTRIBUTIONAL RANKING POSITIONS

In this section, the same announcement events are analysed as in the previous section (see Table 1). The companies' stock prices were recorded for the 50 trading days between 140 and 90 trading days prior to the announcement day (training window), the day of the announcement and the day following the announcement (day 0 and +1). Individual daily returns were calculated using equation (1). In total, 50 daily returns from the [-140; -90] period and 2 daily returns from the [0; +1] period were calculated for each of the 403 announcement events. For the NASDAQ Assets, similar sets of daily returns were calculated for the ^NBI and ^IXIC. For the NYSE Assets, similar sets of daily returns were calculated for the ^DRG and ^NYA (Figure 7).

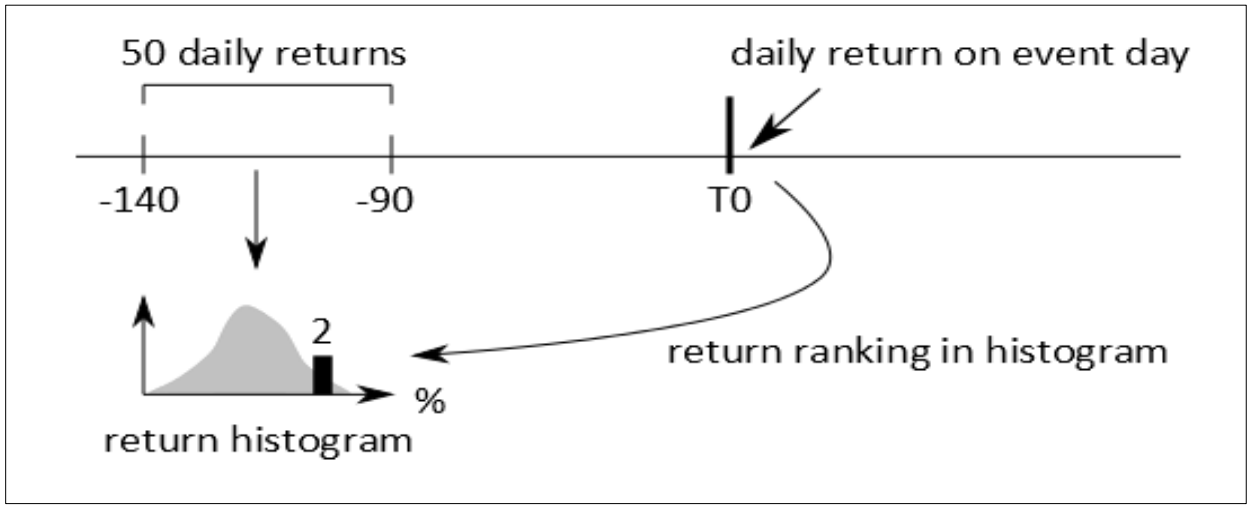

Figure 7: Overview of the strategy used to determine the ranking position of the event window return in a distribution of historical returns obtained in the training window.

For each of the announcements, the 50 daily returns of the Assets and the Indexes were ordered from smallest to largest. The event window return was obtained by taking the largest (smallest) daily return in

the event window in the case of a positive (negative) FDA or EMEA announcement. This procedure allows one single return value to be obtained for the two-day event window. Once this event window return was obtained, the ranking position of this return in the training window returns was determined. A rank value between 0 and 50 was obtained where rank 0 indicates the event associated daily return is larger than any of the observed daily returns in the 50 day window and rank 50 indicates the daily return is smaller than any of the observed daily returns in the 50 day window.

5.1.2. STATISTICAL TESTING

Given all the individual ranks (for both the Assets and the Indexes) for each of the event types (e.g. positive FDA – NASDAQ), a new distribution was built for both the Asset ranks and the Index ranks. These two distributions were then compared using an ordinal Wilcoxon rank-sum test. In the case where the distribution of Asset ranks is statistically smaller (larger) than the distribution of Index ranks, the daily returns on the announcement day or the day following the announcement can be considered exceptionally large (small) given the historical distribution of both Asset and Index returns.

5.2. RESULT & DISCUSSION

The previous section demonstrated there are too few negative EMEA announcements to be analysed in a meaningful way. Consequently negative EMEA announcements will not be investigated in this section.

5.2.1. FDA - NASDAQ

Earlier results suggested FDA announcement have a significant and instantaneous impact on NASDAQ Assets (see Figure 3 for example). Indeed, of the 48 positive FDA announcements under study, 15 (31%) announcements caused a daily stock return on day 0 or +1 larger than any daily stock return observed in the training window (hence have a rank of 0). Thirty-one (65%) of the announcements caused a daily stock return which ranks in the top 10 of the returns observed in the training window (see top left panel in Figure 8). The full distribution of ranks is clearly positively skewed (skewness = 1.095785) towards smaller ranks, indicating returns are on average larger than observed in the training window.

The distributions of corresponding ranks of the ^NBI and ^IXIC are both relatively flat. This is expected as there is no reason to assume daily returns of the indexes on the announcement day to differ from historically observed returns in the training window (see top right panel in Figure 8). The ^NBI returns for positive FDA announcements are slightly skewed towards low ranks (skewness = 0.243982) as the biggest return of day 0 and +1 was taking as the event window return. Testing using an ordinal Wilcoxon

rank-sum test showed that the ranks of the FDA positive NASDAQ Assets are statistically lower than the ranks of both the ^NBI and ^IXIC index (Table 4). It is important to note that analysing event day 0 and +1 separately does not yield significant results (see Appendix 9), indicating that FDA announcements do happen both during the trading day (day 0) and after the close of the trading day (day +1) and, as a consequence, both days of the announcement window need to be analysed together.

Table 4: P-values of distribution testing using Wilcoxon rank-sum tests. Ranks of Asset returns in the announcement event window in a distribution of traning window returns were compared to ranks of Index returns.

		FDA		EMA	
Asset type	**Index**	**Positive**	**Negative**	**Positive**	**Negative**
NASDAQ	NBI	0.000087*	0.000152*	0.664700	-
	IXIC	0.000073*	0.000361*	0.984960	-
NYSE	DRG	0.256340	0.594988	0.598380	-
	NYA	0.585980	0.975524	0.683640	-
NYSE Big Pharma†	DRG	0.826760	-	0.409500	-
	NYA	0.299700	-	0.594460	-
NYSE Standard‡	DRG	0.516920	-	0.567700	-
	NYA	0.448480	-	0.877140	-

† Indicates a subsample of the Big Pharma companies (see Appendix 1)

‡ Indicates standard approvals defined as NDA 'type 1' and review classification 'Standard' for FDA products; no generic, no biosimilar, no orphan for EMA products.

* Indicates statistically significant results at the 5% level.

Similar results are obtained when analysing the stock responses of NASDAQ listed companies to negative FDA decisions. Of the 43 negative FDA announcements under study, 20 (47%) have returns smaller than all the observed returns in the training window. 30 announcements (70%) are associated with returns which rank in the bottom 10 of the returns observed in the training window (Figure 8). The full distribution of ranks is clearly negatively skewed (skewness = -1.161189) towards larger ranks. Testing using an ordinal Wilcoxon rank-sum test showed the ranks of the returns of the NASDAQ assets are significantly larger than the return ranks of the ^NBI and ^IXIC (Table 4). In contrast to the positive FDA announcements, analysing event day 0 and +1 separately yields significant results as well (p-values are 0.0402 and 0.0231 respectively), also see Appendix 9.

Although there is a significant stock price anticipation leading up to the actual FDA announcement, there still is a significant stock price reaction following both positive and negative announcements[16]. This clearly opens the window for profitable short-term trading opportunities. Market participants could 'place their bets' by buying (shorting) a stock prior to the predetermined FDA announcement date and hope for a positive (negative) outcome[17]. However, one should bear in mind that the 'trading and hoping' strategy generally will only generate a profit when systematically more predictions are correct than wrong. It is clear that any information regarding the outcome can be beneficial for market participants (either by being long in case of a positive outcome or short in case of a negative outcome) and discretion by the members of the FDA voting panel is of utmost importance to ensure a fair market environment where all participants have symmetrical information.

Furthermore, there appears to be no strict form of market efficiency. Although there is a lot of public information regarding the clinical trials submitted to the FDA, the market is systematically anticipating a positive outcome. As a consequence, negative FDA announcements come more as a shock as the observed negative returns following a negative announcement are extremer than the returns observed following a positive announcement. This can be explained by the fact that positive news probably will generate positive cash flows in the future, but this does not necessarily mean the company will become a very profitable multi-billion company. However, negative news in many cases means there is a certainty of no future cash flows and consequently dilutive financing rounds to continue existing operations are likely or even bankruptcy. This assymetry in responses to positive and negative news has been demonstrated several times before (Sarkar and de Jong 2006).

5.2.2. FDA – NYSE

Compared to the instantaneous impact of FDA announcements on NASDAQ Assets, the impact on NYSE Assets is relatively limited. Of the 140 positive announcements under study, only 6 (4.2%) are associated with a daily stock return on day 0 or +1 larger than any daily stock return observed in the training window. Forty-five (32%) of the announcements are associated with a daily stock return which ranks in the top of the returns observed in the training window (Figure 8). The positive skew of the distribution is

[16] The distribution of daily NASDAQ returns is leptokurtic (i.e. they have "fat tails") under normal circumstances and the FDA announcements still cause tail-events. Standard risk prediction and Value-at-Risk (VaR) models assuming normal distibutions are clearly not a good option to assess the risk of NASDAQ listed life science companies.

[17] FDA announcement dates are typically known in advance and are listed on specialised websites such as RTTnews: http://www.rttnews.com/corpinfo/fdacalendar.aspx.

largely attributable to the method used to determine a single ranking value in the two day announcement event window (see Appendix 9).

The distribution of corresponding ranks of the ^DRG and ^NYA is relatively similar to the distribution of the ranks of the NYSE Assets. Testing using an ordinal Wilcoxon rank-sum test showed that the ranks of the FDA positive NYSE Assets are statistically not different from the ranks of both the ^NBI and ^IXIC (Table 4). Analysing decisions on Big Pharma companies (as defined in Appendix 1), standard product announcements, and analysing day 0 and day +1 separately does not yield statistical significant results (Table 4).

Similar results are obtained when analysing the stock responses of NYSE listed companies to negative FDA decisions (Table 4). However, as there are only 7 observations available, it is difficult to draw conclusive results from this dataset.

Apparently, the market is more efficient in respect to NYSE listed companies. FDA announcement are more anticipated and come less as a shock and as a result do not cause extreme daily returns. However, one should keep in mind that large pharmaceutical companies, typically listed on NYSE, constantly report news on products under development, clinical trial results, products filed etc. As a consequence, the distribution of daily returns in the training window might contain event-driven returns which in turn makes it more difficult to identify 'extreme' returns following an FDA announcement.

However, it is more likely that other, more fundamental, explanations can explain these observations. As mentioned before, NYSE listed life science companies have a plentitude of products on the market and in the pipeline, making the impact of one single new product relatively limited. Furthermore, the FDA approval process is the final step in a long process of product development which is clearly communicated to the markets. This will be discussed in more detail in the following section.

Alos, large pharmaceutical companies are better covered by analysts[18] than smaller NASDAQ companies, resulting in a greater market efficiency and a smaller surprise effect following the announcement (Canivet 2010; Guagliano, Linciano et al. 2013).

[18] It is estimated that 35 – 40% of all publicly traded companies worldwide have no sell-side analyst coverage. Unfortunately, it is the smaller, less liquid companies that tend to slip through the cracks. More heavily traded, large-cap companies attract greater sell-side analyst interest.

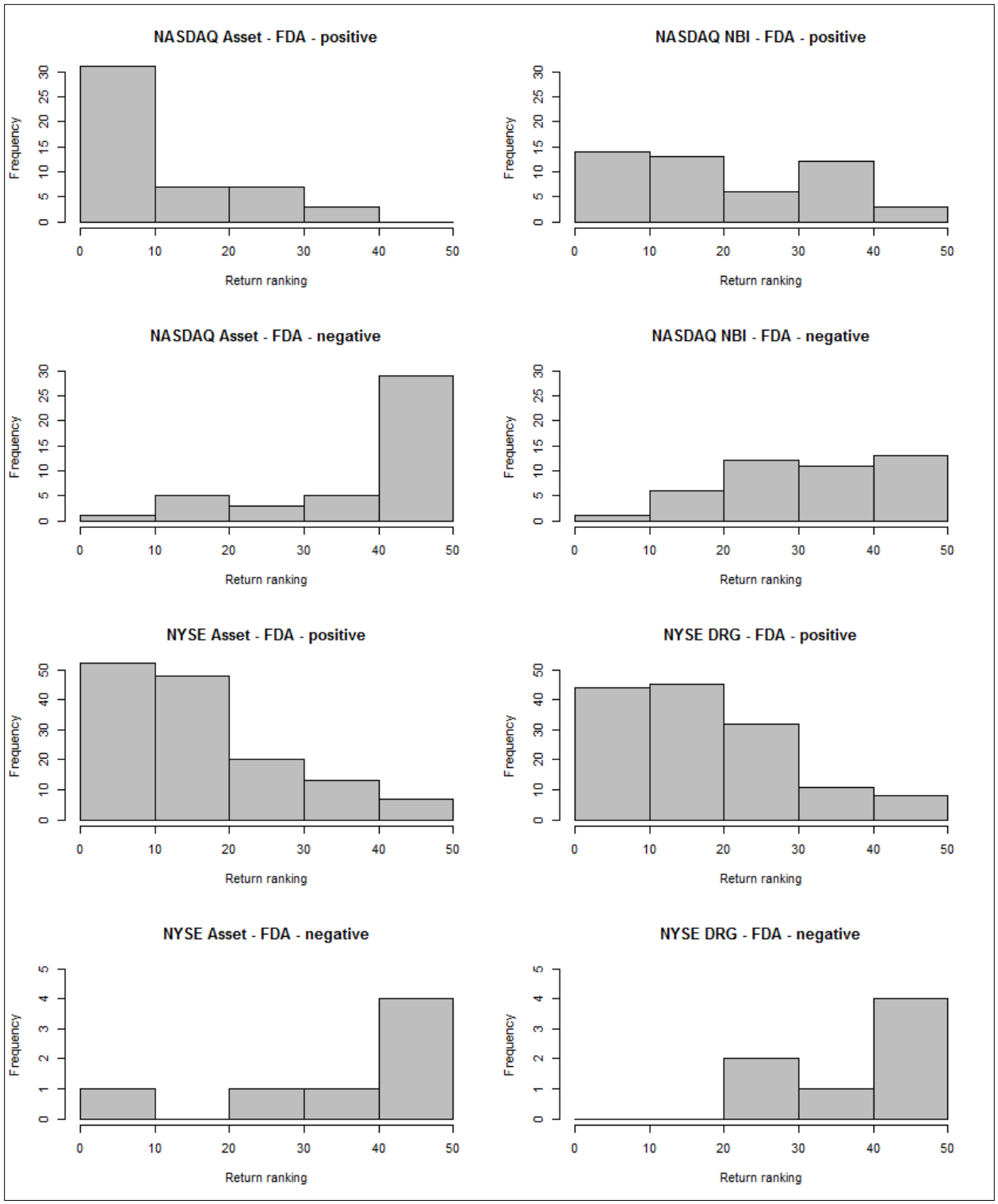

Figure 8: Histogram of the ranks of the daily returns on FDA announcement day 0 / +1 in a distribution of daily returns obtained 140 days to 90 days prior to the announcement day. The histogram under NASDAQ Asset corresponds to the distribution of ranks of the companies under study, NBI indicates NASDAQ Biotechnology Index and corresponds to the distribution of ranks of this index, DRG indicates NYSE Pharmaceutical Index and corresponds to the distribution of ranks of this index.

5.2.3. EMEA

Compared to the instantaneous impact of FDA announcements on the stock prices of NASDAQ listed companies, the impact of EMEA annoucements on NASDAQ listed companies is less clear. The distribution of both the FDA positive NASDAQ Assets and the Index ranks are skewed towards smaller values (Figure 9) and do not differ statistically (Table 4). Results are also not significant for day 0 ($p = 0.5718$) and day +1 ($p = 0.6647$) separately.

Results are not significant possibly due to the relatively limited number of observations and thus lower power of statistical testing. Furthermore, the CHMP Opinion issued around day -50 in the training window might cause the real announcement effect to be captured in the training window, making it more difficult to have an even more skewed distribution. This in turn complicates capturing the event at day 0 or day -1.

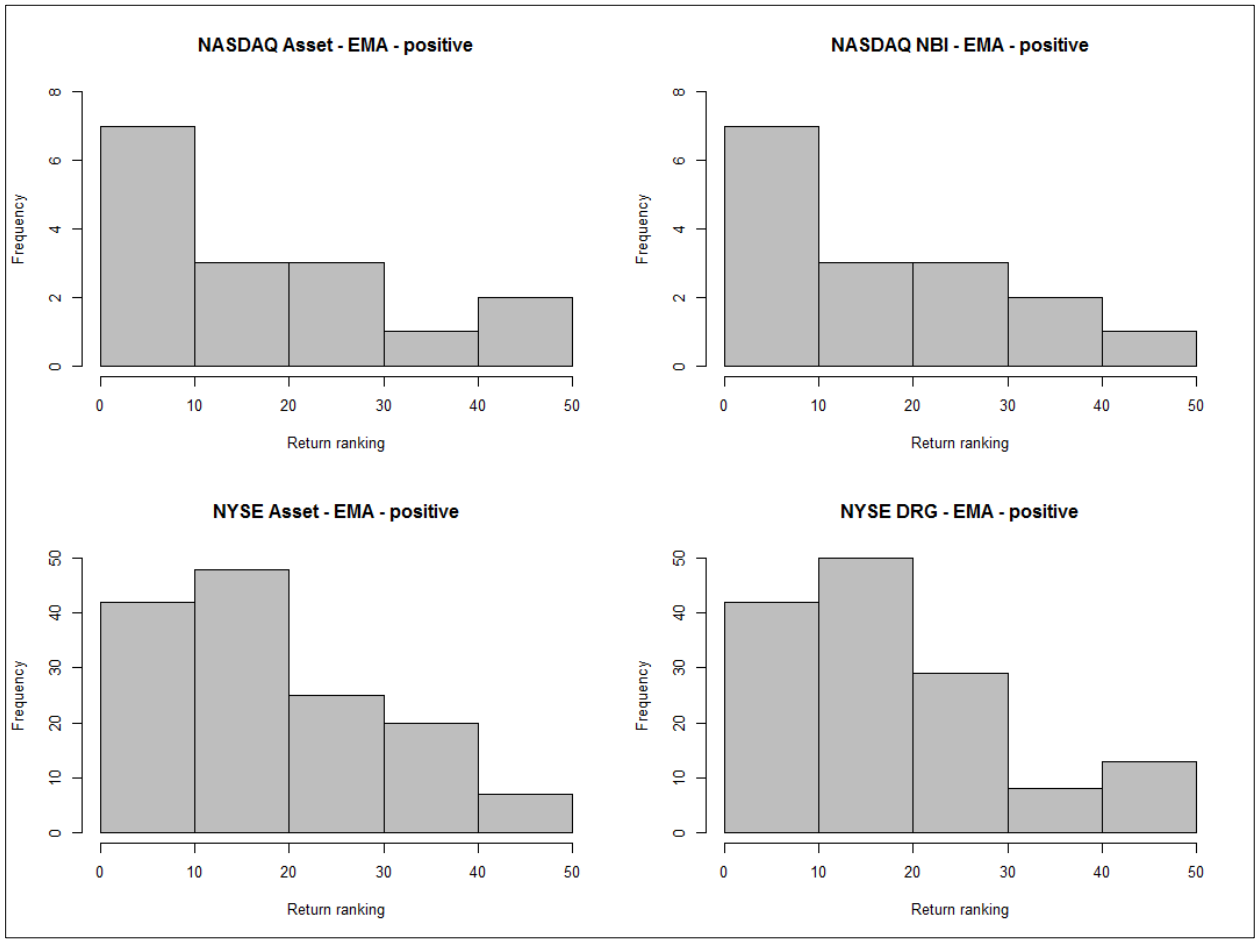

Figure 9: Histogram of the ranks of the daily returns on EMA announcement day 0 / +1 in a distribution of daily returns obtained 140 days to-90 days prior to the announcement day. The histogram under NASDAQ Asset corresponds to the distribution of ranks of the companies under study, NBI indicates NASDAQ Biotechnology Index and corresponds to the distribution of ranks of this index, DRG indicates NYSE Pharmaceutical Index and corresponds to the distribution of ranks of this index.

Similar to the absence of a clear instantaneous response of NYSE listed companies to positive FDA announcements, NYSE listed companies do not respond to EMEA announcements. Of the 142 positive announcements under study, only 3 (2.1%) are associated with daily stock returns on day 0 or +1 larger than any daily stock return observed in the training window. Thirty-nine (27.5%) of the announcements are associated with a daily stock return which ranks in the top 10 of the returns observed in the training window (Figure 9). Again, the positive skew of the distribution is largely attributable to the method used to determine a single ranking value in the two day announcement event window (data not shown).

The distribution of corresponding ranks of the ^DRG and ^NYA is similar to the distribution of the ranks of the NYSE Assets. Testing using an ordinal Wilcoxon rank-sum test showed that the ranks of the FDA positive NYSE Assets are statistically not different from the ranks of both the ^NBI and ^IXIC (Table 4). Analysing decisions on Big Pharma companies (as defined in Appendix 1) and standard product announcements does not yield statistical significant results (Table 4).

5.3. CONCLUDING REMARKS

Public NASDAQ listed companies show exceptional daily stock price returns following an FDA announcement. Positive FDA announcements result in exceptional positive dialy stock returns unobserved in a 50 day period preceding the announcement. Negative FDA announcement result in exceptional negative stock price returns. The returns are asymetrical; negative FDA announcements result in more negative returns than positive announcements results in positive returns.

NYSE listed companies show no exceptional daily stock returns following FDA announcements. Both NASDAQ and NYSE listed companies show no exceptional daily stock returns following EMEA announcements. This difference between FDA and EMEA announcements is possibly attributable to the existing differences between the FDA and EMEA reviewing process.

Further investigation could focus on a more detailed subsampling of the products developed by NYSE listed companies. It is to be expected that FDA announcements regarding highly profitable products (e.g. diabetes, cancer, ageing drugs) developed by big pharmaceutical companies might cause a different stock price response compared to products with only a limited market potential (e.g. generics).

6. EVENT STUDY ANALYSIS

The previous two sections focussed on stock price anticipation over a relatively long horizon and the exceptionality of stock price responses on the announcement day. This section will focus on stock price anticipation in a short period preceding the actual FDA or EMEA announcement, the return on the announcement day, and the return in the period following the announcement day using an event study framework. The event study framework corrects biasses present in earlier analyses such as global market returns and company specific market return exposure.

6.1. METHODOLOGY

Event studies can be used to measure the effect of an event – economic or firm specific – on the value of a firm (MacKinlay 1997). Typical examples include the effect of a change in the regulatory environment (Schwert 1981) or the effect of merger announcements on public stock prices (Weston and Halpern 1983). However, event studies have also been used in the past to study the effect of FDA decisions on public stock prices (Sarkar and de Jong 2006).

An event study typically involves four steps (De Jong 2007): 1) Specification of an event of interest and identification of the accompanying timing, 2) determination of normal behaviour of the stock price using a benchmark model, 3) determination of excess (abnormal) returns around the timing of the event of interest using the information gathered in the benchmark model, and 4) testing these abnormal returns for statistical significance.

I will describe these four steps into more detail in the following paragraphs. These paragraphs are roughly based on event study work carried out by MacKinlay and de Jong (MacKinlay 1997; De Jong 2007).

6.1.1. SPECIFICATION OF EVENT TIMING

The announcements dates are clearly specified in the FDA and EMEA datasets. The training window to determine benchmark behaviour is defined from 140 to 90 trading days prior to the announcement date. The anticipation window is defined from 60 days to 1 day prior to the announcement date. The event window is defined from the announcement day to 1 day past the announcement day. The post-announcement window is defined from 2 days past the announcement to 30 days past the announcement (Figure 2).

6.1.2. DETERMINING BENCHMARK BEHAVIOUR

Using data from the training window, normal behaviour of the stock returns can be determined. Many different models exist to determine this normal behaviour. One of the easiest models frequently used is the mean-adjusted model where (daily) returns are averaged over the entire training window period, from $T1$ to $T2$. The normal return NR_{it} of stock i on time t is then given by:

$$NR_{it} = \frac{1}{T} * \sum_{t=T1}^{T2} R_{it} \tag{6}$$

where T equals the length of the training window and R_{it} the return of stock i on time t.

Although this methodology has been used in the past (De Jong 2007) and seems reasonable at first sight, market-wide stock movements are not captured by this model. Imagine a situation where a drug were approved amidst a downward market trend. Although the stock price might decline, it could still be outperforming the market, thus generating positive abnormal returns and, indeed, signalling a positive response to the announcement event. To overcome this limitation inherent to the mean-adjusted model, rather than using stock-specific averaged returns, market-adjusted returns can be used. The normal return NR_{it} of stock i on time t is then given by:

$$NR_{it} = R_{mt} \tag{7}$$

where R_{mt} is the return of an appropriate market index on time t. However, this assumes each stock reacts to global market information in a similar fashion.

The Capital Asset Pricing Model (CAPM), developed by, amongst others, Treynor (French 2003) and Sharpe (Sharpe 1964) built further on the seminal work of Markowitz regarding diversification and modern portfolio theory (MPT) (Markowitz 1952). CAPM states the expected return of an individual asset depends on the risk-free rate (R_f), the return of a global market index (R_m), a factor loading (β) which indicates how strong a particular stock responds to market returns, and an intercept (α), of which the expected value is 0.

Market-adjusted return models assume the β of each stock equals exactly 1 and, as a consequence, that each stock responds in a similar fashion to market driving events. A simple factor model similar to CAPM explains the returns for stock i using the following equation:

$$R_i = \alpha_i + R_f + \beta_i * (R_m - R_f) + \varepsilon_i. \tag{8}$$

As the risk free rate was virtually zero in the period under consideration, equation (8) can be simplified to the following single-factor index model:

$$R_i = \alpha_i + \beta_i * R_m + \varepsilon_i \quad (9)$$

where ε_i represents an estimation error term or disturbance term which is 0 on average. This equation can be estimated using ordinary least squares (OLS) regression. According to the single-factor index model, normal returns of stock i on time t are a function of the estimated response to market returns ($\widehat{\beta_\iota}$) and the estimated intercept ($\widehat{\alpha_\iota}$):

$$NR_{it} = \widehat{\alpha_\iota} + \widehat{\beta_\iota} * R_{mt} \quad (10)$$

where R_{mt} is the return of an appropriate index on time t(see Table 2).

More complex models have been proposed in the past. For example, the Fama-French model uses three factors, compared to the standard single-factor model (Fama and French 1993). Fama and French observed that companies with a small market capitalization and companies with a high book-to-market (BTM) ratio tend to perform better (MacKinlay 1997). Consequently, they added two factors to reflect exposure to these two classes and proposed the following model:

$$R_i = \alpha_i + R_f + \beta_i * (R_m - R_f) + b_{si} * SMB + b_{vi} * HML \quad (11)$$

where SMB stands for *small minus big* and HML for *high minus low*; these variables measure respectively (historic) excess returns of small market capitalization companies (small caps) over big caps and of companies with a high book-to-market (BTM) over low BTM companies[19]. The coefficients $b_{si}$and b_{vi} correspond with the exposures of stock i to these two factors. Again, this model can be simplified assuming a risk free rate of zero. The following equation can then be estimated using OLS:

$$R_i = \alpha_i + \beta_i * R_m + b_{si} * SMB + b_{vi} * HML + \varepsilon_i \quad (12)$$

which yields the following equation for the normal returns of stock i on time t:

$$NR_{it} = \widehat{\alpha_\iota} + \widehat{\beta_\iota} * R_{mt} + \widehat{b_{s\iota}} * SMB_t + \widehat{b_{v\iota}} * HML_t. \quad (13)$$

More complex (higher number of factor) models have been proposed. For example, Chen Roll and Ross proposed a multi-factor model where the following factors are used: unanticipated growth in industrial

[19] HML and SMB data is available from the data library website of Kenneth French: http://mba.tuck.dartmouth.edu/pages/faculty/ken.french/data_library.html.

production, changes in expected inflation, unexpected inflation, default spread, term spread, and the return on the equal-weighted and value-weighted market portfolio (Chen, Roll et al. 1986).

Recently, Makarov and Papanikolaou used a principal components approach to propose an industry specific four-factor model using the following four factors: the return on the value-weighted market portfolio, the return of capital minus consumption goods producers, the return of cyclical minus non-cyclical industries, and the return of input good producers minus everyone else (Makarov and Papanikolaou 2007). However, MacKinlay has demonstrated there is little benefit to be obtained in moving from a single factor model to a multi-factor model when trying to predict or explain returns, unless the sample firms have a common characteristic such as market capitalization or industry type (MacKinlay 1997).

A slight modification of the Fama-French model has been used in an event study by Bastin and Hübner to test the effect of three important events in spring 2000. Two political statements by Bill Clinton and Tony Blair had a major impact on biotechnology stocks as there was uncertainty about the strength of genomics based patents. A breakthrough announcement by Celera Genomics had a significant impact as it opened to door to the genomics era[20]. The three original factors of the Fama-French were extended with a fourth factor defined as the 'patent market value' of a firm which was calculated as the ratio between the firm's market value of equity in excess of total cash and the number of patents (Bastin and Hübner 2006).

6.1.3. ESTIMATING ABNORMALS RETURNS

The abnormal return of stock i on time t (AR_{it}) is defined as the difference between the observed return and the normal return return calculated using one of the proposed benchmark:

$$AR_{it} = R_{it} - NR_{it}. \tag{14}$$

Using for example the Fama-French model from equation (10), the abnormal return is given by:

$$AR_{it} = R_{it} - \widehat{\alpha_i} - \widehat{\beta_i} * R_{mt} - \widehat{b_{si}} * SMB_t - \widehat{b_{vi}} * HML_t \tag{15}$$

[20] The three events followed each other very rapidly and the first two fount their origin in the announced publication of the first human genome by Celera. On 14 March 2000 Bill Clinton and Tony Blair recommended free access to raw genomic data, but recognize intellectual property protection for gene-based invention. On 5 April 2000 Bill Clinton reaffirms his previous statement, but specifies that commercial applications should be protected by patents and 6 April 2000 Celera Genomics announced its completion of the sequencing phase of the human genome.

which corresponds with the estimation error (ε_i) from equation (9). In other words, the abnormal return is the part of the observed return which could not be predicted using a specific benchmark model.

Consider a sample of N events which starts on t_0 and runs for a period T, hence the abnormal return of stock 1 on the event date can be denoted as $AR_{1,0}$. The abnormal return of the N^{th} stock on the event date can be denoted as $AR_{N,0}$. The abnormal returns can then be represented in the following matrix notation:

$$\begin{bmatrix} AR_{1,0} & AR_{2,0} & \cdots & AR_{N,0} \\ AR_{1,1} & AR_{2,1} & \cdots & AR_{N,1} \\ \vdots & & \ddots & \vdots \\ AR_{1,T} & AR_{2,T} & \cdots & AR_{N,T} \end{bmatrix}. \quad (16)$$

Each row of this matrix represents a cross-sectional overview of the abnormal returns on a specific time whereas each column represents a time series of abnormal returns for a specific stock.

Assuming the training window is large (MacKinlay 1997), the variance of the abnormal return of stock i on time t can be estimated by:

$$\widehat{\sigma^2}(AR_{it}) = \frac{1}{T-1} * \sum_{s=T1}^{T2} (AR_{is} - \overline{AR_i})^2 \quad (17)$$

where $\overline{AR_i}$ is the average abnormal return for stock i over the training window. As the abnormal return in the training window equals the estimation error ε_i and OLS, by design, equalises the expected estimation error to zero, equation (17), under the assumption of no serial correlation, simplifies to:

$$\widehat{\sigma^2}(AR_{it}) = \frac{1}{T-1} * \sum_{s=T1}^{T2} {AR_{is}}^2 \quad (18)$$

which is equal to saying that the estimated variation of the abnormal returns on every time t is, assuming homoscedasticity, equal to the sum of squared estimation residuals obtained in the training window divided by T-1.

The parameters described above correspond to a single observation of the abnormal return matrix shown in equation (16). However, a single observation of abnormal returns might be distorted by other factors influencing the stock price. Abnormal returns can be aggregated over the time and the observation dimension of the abnormal return matrix to vastly the performance of event studies. For example, abnormal returns can be averaged over different observations (i.e. different FDA/EMEA

announcements). The unweighted cross-sectional average abnormal returns on time t are then simply given by:

$$\overline{AR_t} = \frac{1}{N} * \sum_{i=1}^{N} AR_{it} \tag{19}$$

and the variance associated with this average abnormal return, assuming all abnormal returns are cross-sectionally uncorrelated and cross-sectionaly homoscedastic on time $t (\sigma_{it} = \sigma)$, is:

$$\widehat{\sigma^2}(\overline{AR_t}) = \frac{1}{N^2} * \sum_{i=1}^{N} \widehat{\sigma^2}(AR_{it}) = \frac{1}{N} * \widehat{\sigma^2}. \tag{20}$$

However, often one is not interested in the (average) abnormal returns on a given time t, but rather in the cumulative abnormal return over a certain period. Consider for example the anticipation period prior to the announcement date; the abnormal return on a specific moment in the anticipation window is not very informative, however, the cumulative abnormal return on a specific time-point is. Cumulative abnormal returns for a single stock i for the period $[T1, T2]$ are given by:

$$CAR_{i;T1,T2} = AR_{i,T1} + AR_{i,T1+1} + AR_{i,T1+2} + \cdots + AR_{i,T2} = \sum_{t=T1}^{T2} AR_{it}. \tag{21}$$

Similarly, cumulative returns can be calculated by aggregating average returns over time. Cumulative average abnormal returns can also be obtained by cross-section ally aggregating cumulative abnormal returns. For example, the average cumulative abnormal return for a sample of N events over the period $[T1, T2]$ is given by:

$$\overline{CAR}_{T1,T2} = \sum_{t=T1}^{T2} \overline{AR_t} = \frac{1}{N} * \sum_{i=1}^{N} CAR_{i;T1,T2}. \tag{22}$$

As the variance of a sum of parameters is the sum of the variances (remember no serial correlation was assumed), the variance of cumulative abnormal return for stock i over the period $[T1, T2]$ is:

$$\widehat{\sigma^2}\left(CAR_{i;T1,T2}\right) = (\mathrm{T2} - \mathrm{T2} - 1) * \widehat{\sigma^2}(AR_{it}). \tag{23}$$

Similarly, the variance of the cumulative average abnormal return over the period $[T1, T2]$ is:

$$\widehat{\sigma^2}\left(\overline{CAR}_{T1,T2}\right) = (\mathrm{T2} - \mathrm{T1} - 1) * \widehat{\sigma^2}(\overline{AR_t}). \tag{24}$$

Up until now, the variance was assumed to be homoscedastic over the time dimension, but also cross-sectional. This assumes all abnormal returns of the matrix in equation (16) have the same variance. This assumption is too strong and can easily be corrected (De Jong 2007). Rather than using the abnormal return, the normalized abnormal return of stock i at time t can be defined as follows:

$$NAR_{it} = \frac{AR_{it}}{\hat{\sigma}(AR_{it})} \ . \tag{25}$$

where the abnormal return can be calculated using the single-factor model or the Fama-French model. The estimated standard deviation can be calculated using the abnormal returns in the training window according to equation (18). Equation (25) effectively normalizes the standard deviation of the abnormal returns to 1.

Different observations at time t can now easily be aggregated and averaged over N observations to an average normalized abnormal return at time t. The variance of this normalized average abnormal return is still assumed homoscedastic over time and equal to:

$$\widehat{\sigma^2}(\overline{NAR_t}) = \frac{1}{N}. \tag{26}$$

6.1.4. Statistical testing for significance

Individual abnormal returns can be tested for statistical significance, under the null hypothesis of no abnormal returns:

$$\mathrm{H_0}: \mathrm{AR_{it}} = 0 \tag{27}$$

using the following test-statistic, assuming the training window is large:

$$Z = \frac{AR_{it}}{\sqrt{\widehat{\sigma^2}(AR_{it})}} \sim N(0,1) \tag{28}$$

where abnormal returns and estimated variance can be calculated using for example equation (15) and (18) respectively.

Average abnormal returns can be tested for statistical significance, under the null hypothesis of no average abnormal returns:

$$\mathrm{H_0}: \overline{\mathrm{AR_t}} = 0 \tag{29}$$

using the following test-statistic:

$$t = \sqrt{N} * \frac{\overline{AR_t}}{\hat{\sigma}} \sim t_{N-1} \approx N(0,1) \tag{30}$$

where $\hat{\sigma}$ corresponds to the estimated variance of a single observation which can be calculated using equation (18). Daily stock returns typically do not follow a normal distribution, but are rather leptokurtic or 'fat tailed'.

This means equation (30) does not hold the proposed distribution, in theory. However, under the assumptions the components of the average abnormal return have the same variance and N is large, the test-statistic follows a normal distribution asymptotically.

Cumulative average abnormal returns for the period $[T1, T2]$ can be tested for statistical significance, under the null hypothesis of no cumulative average abnormal returns:

$$\mathrm{H}_0: \overline{\mathrm{CAR}}_{T1,T2} = 0 \tag{31}$$

using the following test-statistic:

$$t = \sqrt{N} * \frac{\overline{CAR}_{T1,T2}}{\hat{\sigma} * (T2 - T1 - 1)} \sim t_{N-1} \approx N(0,1)\,. \tag{32}$$

As demonstrated before, the assumption of cross-sectional homoscedasticity is too strong. However, abnormal returns can easily be normalized to have cross-sectional homoscedasticity and a variance of 1. Both equation (30) and (32) assume cross-sectional homoscedasticity and can be altered to take normalized abnormal returns into account.

The test-statistic for the normalized average abnormal return becomes:

$$t = \sqrt{N} * \frac{\overline{NAR_t}}{1} \sim t_{N-1} \approx N(0,1) \tag{33}$$

and the test-statistic for the normalized cumulative average abnormal return becomes:

$$t = \sqrt{N} * \frac{\overline{NAR_{T1}} + \overline{NAR}_{T1+1} + \cdots + \overline{NAR}_{T2}}{T2 - T1 - 1} \sim t_{N-1} \approx N(0,1)\,. \tag{34}$$

6.2. Results and discussion

6.2.1. Model selection

As outlined above, normal (benchmark) returns can be calculated using different models and different reference indexes. Switching from a single-factor model to the Fama-French model always improves the

average coefficient of determination obtained in the regressions when using NASDAQ Assets data. Besides the two standard reference indexes used in the previous sections (^NBI and ^IXIC), an additional reference index was tested; the NASDAQ Health Care index (^IXHC). Both in the single-factor model and the Fama-French model, using ^NBI gives the best results (Figure 10). The best coefficient of determination for the NYSE Assets is obtained using the Fama-French model and the ^DRG (data not shown). Consequently, analyses are carried out using the Fama-French model using either ^NBI or ^DRG.

The training window is defined from 140 to 90 trading days prior to the announcement date. Due to data availability problems and the inclusion of an anticipation window, the training window is relatively short. Other event studies often use longer training windows or training windows which are located a longer period of time prior to the event of interest (De Jong 2007). However, for the stocks where data was available in longer training windows it was verified that regression results, using the Fama-French model with the ^NBI or ^DRG, do not change dramatically when changing both the length and the location of the training window (see Appendix 10).

6.2.2. FDA - NASDAQ

Cumulative average abnormal returns ($\overline{\mathrm{CAR}}$) in the anticipation window (starting at day -60) are similarly positive for both the FDA positive and FDA negative NASDAQ Assets. However, in both cases cumulative returns are not significantly larger than 0 (data not shown). The cumulative average abnormal return calculated using both positive and negative announcements is also not significantly larger than 0 in the anticipation window (also see Appendix 12). The $\overline{\mathrm{CAR}}(-60, \mathrm{t})$ reaches a minimal p-value at t = -29 (although the p-value is not significant at the 5% level) (see Figure 11).

The results in the anticipation window do differ between positive and negative FDA announcements in approximately the last 10 days prior to the announcement. There is only 1 trading day with a significant abnormal return in the 10 trading days preceding a positive FDA announcement compared to 7 out of 10 in the case of a negative FDA announcement (Table 5). The cumulative abnormal returns are not significantly negative in the case of negative FDA announcement when calculated over the 10 days preceding the announcement. However, when calculating the cumulative abnormal return over a shorter period, values become significantly negative with $\overline{CAR}(-8, -1)$ being 0.0494 and $\overline{CAR}(-2, -1)$ being 0 for example (Appendix 12). These results indicate investors are anticipating the bad news, potentially indicating illegal insider-trading. However, these results clearly go against earlier findings that negative announcements are preceded by significant negative results over a longer horizon

(Rothenstein, Tomlinson et al. 2011). Both positive and negative announcements generate the same positive anticipation and only diverge approximately 8 days prior to the announcement date.

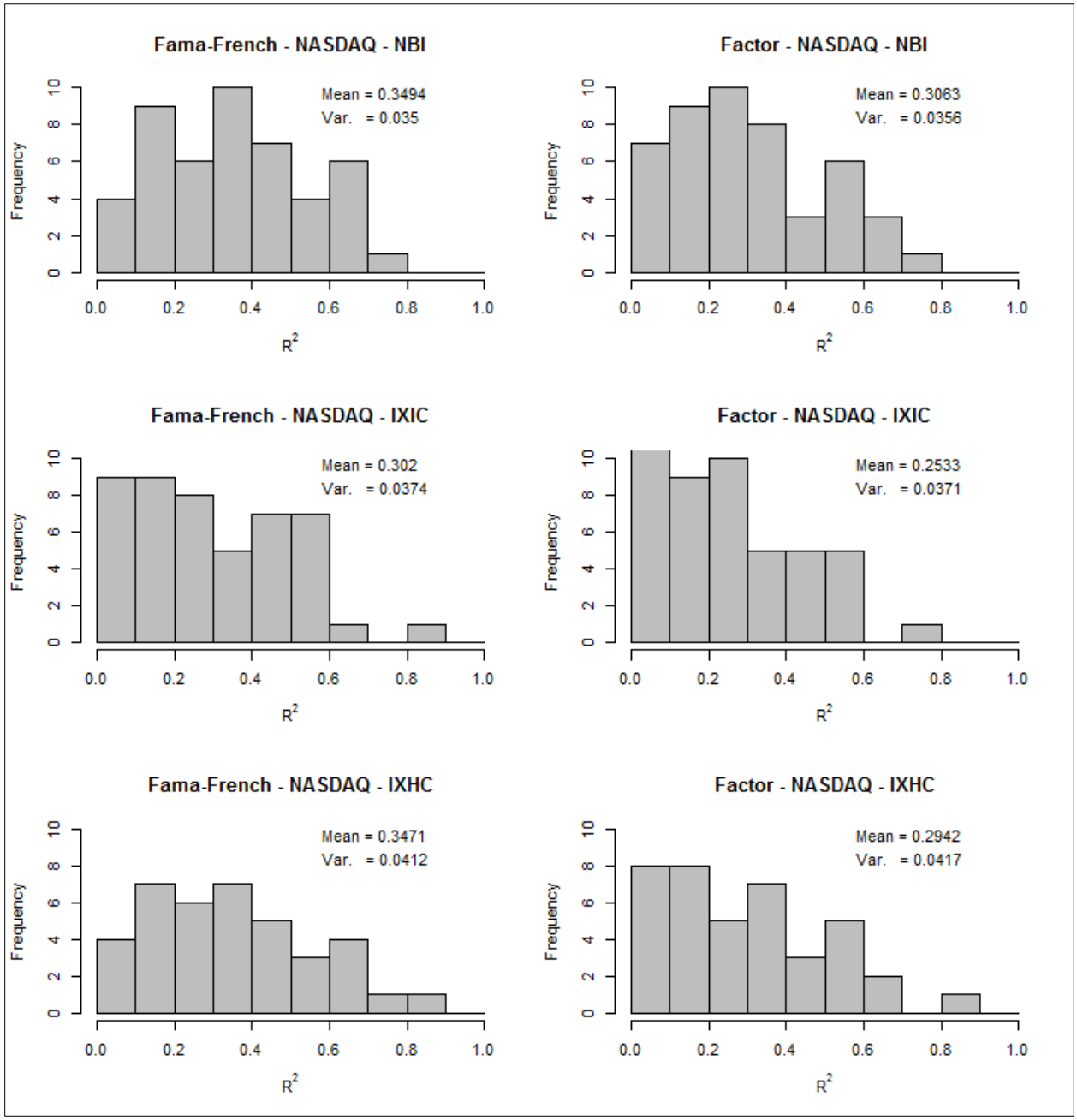

Figure 10: Distributions of R^2-values of different models used to determine benchmark behaviour of NASDAQ returns. 'Factor' indicates where the single-factor model was used, 'Fama-French' indicates where the Fama-French model was used. 'NBI', 'IXIC', and 'IXHC' indicate where the NASDAQ Biotechnology Index, the NASDAQ Composite, and the NASDAQ Health Care Index were used to determine market returns in the models. Mean and variance (Var.) of the distribution are shown in the top right corner of each panel.

In correspondence with the results obtained in earlier sections, there are significant abnormal returns on the announcement day; positive abnormal returns in case of positive FDA announcements, negative

abnormal returns in case of negative FDA announcements. In both cases the test-statistics are very large, confirming earlier findings that daily returns in the announcement window are real tail events with significant wealth effects (Table 5).

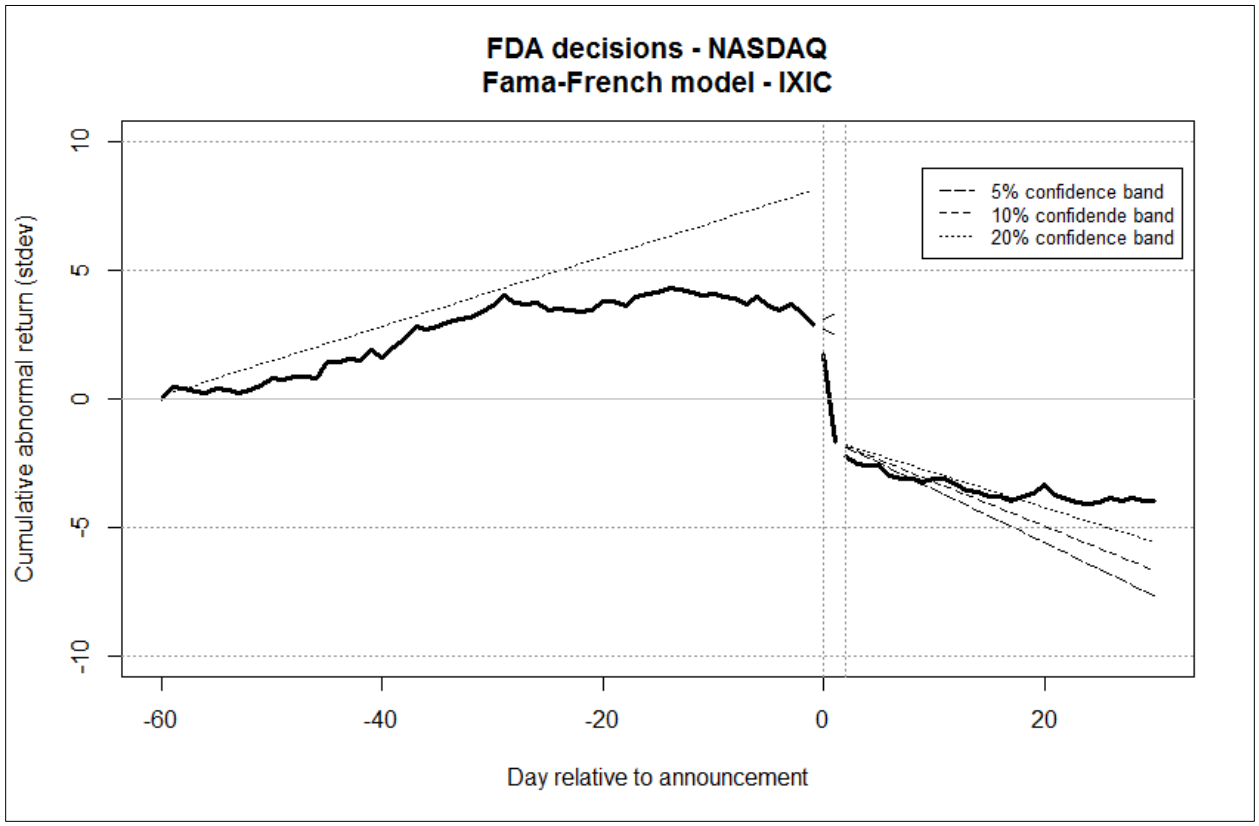

Figure 11: Evolution of the normalized cumulative average abnormal return of FDA positive and negative NASDAQ Assets combined Vertical dashed lines demarcate the anticipation, announcement window, and post-announcement window. Diagonal dashed lines indicate confidence intervals at different levels.

Furthermore, investors seem to be overoptimistic, always. There are significant negative abnormal results up to two trading days following a positive FDA announcement and up to seven days following a negative announcement. These results partially contradict research by Sarkar and de Jong who detected only significant abnormal returns on day 0 and +1 following negative FDA announcements (Sarkar and de Jong 2006). However, other studies have also detected longer period of significant negative abnormal returns following negative FDA announcements (Bosch and Lee 1994).

This also contradcits earlier research results that showed the market is inefficient and investors tend to overreact to dramatic and unexpected news (De Bondt and Thaler 1985). However, my results indicate investors tend to *under*react to negative FDA announcements with significant negative abnormal returns in the aftermath of the negative announcement. The observation that the market is inefficient still does

stand, however. These findings clearly contradict that the market is always efficient and no money is to be made from reversal strategies (Conrad, Gultekin et al. 1997). Other researchers have indicated there are several psychological explanations for this observed inefficiency such as overconfidence and biased self-attribution (Daniel, Hirshleifer et al. 1998). Recent research has also demonstrated that the combination of overreaction to good news and underreaction to bad news is of particular importance for technology stocks, possibly explaining the observed stock price reaction (Akhigbe, Larson et al. 2002).

However, it appears many professional investors are aware of this seemingly inefficient market behaviour. In case of a positive regulatory announcement, public disclosure announcements often indicate large short positions of institutional investors or hedge funds (Remy 2013). These investors often cite reasonably explanations for the initiation of their short position such as overenthusiasm of smaller investors or irrational expectations of the market in regards to the earning potential of developed products.

6.2.3. FDA – NYSE

No significant abnormal individual daily returns are found in the entire anticipation window for FDA positive NYSE Assets. As a consequence, there are also no periods with significant cumulative abnormal returns in the anticipation window (Table 6). Similar insignificant results are obtained for the Big Pharma and Standard subsamples of the positive FDA announcements[21].

There are 3 significant (2 negative and 1 positive) daily abnormal returns in the entire anticipation window for FDA negative NYSE assets. However, there are no significant cumulative abnormal returns close to the announcement date (Table 6).

[21] Both subsamples are defined in the same way as before. See section 4: Stock price anticipation – averaged cumulative returns.

Table 5: Overview of the event study statistics of FDA positive and FDA negative NASDAQ Asset calculated using the Fama-French model and the NASDAQ Biotechnology Index.

Day	Positive				Negative				Positive + Negative			
	Daily		Cumulative		Daily		Cumulative		Daily		Cumulative	
	AR	t	CAR	t	AR	t	CAR	t	AR	t	CAR	t
-10	-0.1032	-0.7152	-0.1032	-0.7152	0.2075	1.3607	0.2075	1.3607	0.0436	0.4159	0.0436	0.4159
-9	-0.0895	-0.6198	-0.1927	-0.6675	-0.2566	-1.6824	-0.0491	-0.1608	-0.1684	-1.6066	-0.1248	-0.5953
-8	-0.1070	-0.7412	-0.2997	-0.6921	-0.0150	-0.0985	-0.0641	-0.1400	-0.0635	-0.6060	-0.1883	-0.5989
-7	-0.1510	-1.0462	-0.4507	-0.7806	-0.3273	-2.1461	-0.3914	-0.6416	-0.2343	-2.2351	-0.4227	-1.0080
-6	0.2242	1.5530	-0.2265	-0.3139	0.2406	1.5775	-0.1508	-0.1977	0.2319	2.2123	-0.1907	-0.3639
-5	-0.2591	-1.7950	-0.4856	-0.5607	-0.2929	-1.9204	-0.4436	-0.4849	-0.2750	**-2.6238**	-0.4658	-0.7406
-4	-0.0346	-0.2395	-0.5202	-0.5149	-0.3245	**-2.1279**	-0.7681	-0.7196	-0.1716	-1.6367	-0.6374	-0.8686
-3	0.1111	0.7696	-0.4091	-0.3543	0.3875	*2.5409*	-0.3807	-0.3120	0.2417	2.3056	-0.3957	-0.4718
-2	0.1270	0.8797	-0.2821	-0.2172	-0.9348	**-6.1301**	-1.3155	-0.9585	-0.3748	**-3.5750**	-0.7704	-0.8166
-1	0.0423	0.2929	-0.2398	-0.1662	-1.1630	**-7.6264**	-2.4785	-1.6253	-0.5273	**-5.0297**	-1.2977	-1.2379
0	0.2505	1.7353	0.2505	1.7353	-2.6363	**-17.2876**	-2.6363	**-17.2876**	-1.1136	**-10.6233**	-1.1136	**-10.6233**
+1	2.1888	**15.1643**	2.4392	**8.4498**	-3.2025	**-21.0000**	-5.8388	**-19.1438**	-0.3587	**-3.4221**	-1.4724	**-7.0227**
+2	-0.3847	**-2.6654**	-0.3847	**-2.6654**	-0.7091	**-4.6500**	-0.7091	**-4.6500**	-0.5380	**-5.1322**	-0.5380	**-5.1322**
+3	-0.2873	-1.9906	-0.6720	-2.3280	-0.3436	-2.2532	-1.0527	**-3.4516**	-0.3139	**-2.9946**	-0.8519	**-4.0634**
+4	0.1797	1.2451	-0.4923	-1.1370	-0.4275	**-2.8035**	-1.4803	**-3.2356**	-0.1072	-1.0229	-0.9592	**-3.0499**
+5	0.0059	0.0408	-0.4864	-0.8425	-0.0975	-0.6391	-1.5777	**-2.5865**	-0.0429	-0.4097	-1.0021	**-2.3899**
+6	-0.1216	-0.8422	-0.6080	-0.8424	-0.5934	**-3.8912**	-2.1711	**-2.8474**	-0.3445	**-3.2864**	-1.3466	-2.5692
+7	-0.2894	-2.0049	-0.8974	-1.0362	0.1822	1.1945	-1.9890	-2.1737	-0.0666	-0.6350	-1.4132	-2.2468
+8	-0.0544	-0.3767	-0.9517	-0.9420	0.0740	0.4853	-1.9150	-1.7939	0.0063	0.0600	-1.4069	-1.9173
+9	-0.1515	-1.0493	-1.1032	-0.9554	0.0693	0.4547	-1.8456	-1.5128	-0.0471	-0.4495	-1.4540	-1.7338
+10	0.1539	1.0665	-0.9493	-0.7307	0.1136	0.7446	-1.7321	-1.2620	0.1349	1.2865	-1.3192	-1.3982
+11	-0.0339	-0.2351	-0.9832	-0.6812	-0.0449	-0.2943	-1.7769	-1.1652	-0.0391	-0.3730	-1.3583	-1.2957
+12	-0.1002	-0.6944	-1.0834	-0.6824	-0.1794	-1.1762	-1.9563	-1.1662	-0.1376	-1.3129	-1.4959	-1.2973
+13	0.0623	0.4317	-1.0211	-0.5895	-0.4795	**-3.1440**	-2.4358	-1.3310	-0.1937	-1.8477	-1.6896	-1.3431
+14	-0.1610	-1.1157	-1.1821	-0.6300	0.0897	0.5881	-2.3461	-1.1834	-0.0426	-0.4060	-1.7321	-1.2710
+15	-0.2008	-1.3912	-1.3829	-0.6844	-0.1077	-0.7060	-2.4538	-1.1493	-0.1568	-1.4957	-1.8889	-1.2871

Dashed lines demarcate the anticipation window, event window, and post-event windows. AR indicates average abnormal returns, CAR indicates cumulative average abnormal returns, t indicates the value of the test-statistic. CAR for the anticipation window are calculated starting at day -10, starting at day 0, and starting at day +2 for the anticipation, event, and post-event window respectively. Dotted underlined values are significant at the 10% level, underlined values at the 5% level, and **underlined bold** values at the 1% level. Critical values were calculated using the normal. All critical values are two-tailed.

There are no abnormal returns in the announcement window for FDA positive NYSE Assets, clearly contradicting earlier research results which detected significant positive results. However, Sarkar and de Jong, in their 2006 study, analysed NASDAQ, AMEX, and NYSE listed companies together. When analysing their results in more detail, they found that the major determinants of the abnormal returns were the market capitalization and the novicity of a firm. Sarkar and de Jong concluded that small companies which successfully developed a new product for the first time experience the highest abnormal returns on the announcement day (Sarkar and de Jong 2006). Clearly, small pharmaceutical and biotech companies listed on the NASDAQ meet these criteria better than large NYSE listed pharmaceutical companies. Recent research has also shown that large pharmaceutical companies, to cope with the patent cliff, are eager to buy small and innovative companies with approved products, rather than developing new products themselves. Small NASDAQ companies with an approved product might be a takeover target, partially explaining the pronounced difference in stock price response to positive FDA announcements between NASDAQ and NYSE listed companies (Armenean 2012).

Furthermore, the final FDA approval resolves only a small degree of uncertainty, as most of this uncertainty is resolved previously while the clinical trial and FDA approval process progresses. Large pharmaceutical companies are especially good in communicating on the progress of their products under development, leading to a low degree of uncertainty regarding the final outcome decision by the FDA (Sarkar and de Jong 2006). As the final outcome is highly anticipated, all information is already priced into the stock price, resulting in no significant abnormal return on the day of the actual announcement. This efficiency also leads to no significant returns or cumulative returns in the period following the FDA announcement.

For negative announcements, suprisingly, a significant positive return is found on day +1, but a significant negative abnormal return on day +2. These results are robust as they are similar when different reference indexes are used in the Fama-French model or even when the single-factor model is used (data not shown). These results clearly contradict intuition and earlier research (Bosch and Lee 1994; Sarkar and de Jong 2006). However, one should bear in mind that only 8 negative FDA announcements were available. The returns on day +1 and day +2 partially offset each other and result in no significant cumulative effect. As observed in the case of positive announcements, and contradicting results observed in the case of the NASDAQ Assets, the behaviour in the post-announcement window is not significant, indicating efficient behaviour. If day +2 is not taken into account the $\overline{CAR}(+3, +15)$ becomes virtually zero (Table 6).

Table 6: Overview of the event study statistics of FDA positive and FDA negative NYSE Assets calculated using the Fama-French model and the NYSE Pharmaceutical Index.

Day	Positive				Positive - Standard				Negative			
	Daily		Cumulative		Daily		Cumulative		Daily		Cumulative	
	AR	t	CAR	t	AR	t	CAR	t	AR	t	CAR	t
-10	-0.0554	-0.1465	-0.0554	-0.6554	-0.0316	-0.1516	-0.0316	-0.1516	-0.6009	-1.5899	-0.6009	-1.5899
-9	0.1064	0.2816	0.0510	0.3019	0.2179	1.0449	0.1863	0.4466	-0.1178	-0.3117	-0.7188	-0.9508
-8	-0.0881	-0.2330	-0.0370	-0.1461	-0.4587	-2.1997	-0.2724	-0.4355	0.1628	0.4307	-0.5559	-0.4903
-7	0.0242	0.0639	-0.0129	-0.0381	0.0244	0.1173	-0.2480	-0.2973	-1.0385	-2.7476	-1.5944	-1.0546
-6	0.0737	0.1951	0.0609	0.1440	0.0344	0.1648	-0.2136	-0.2049	0.6732	1.7810	-0.9213	-0.4875
-5	0.0709	0.1876	0.1318	0.2598	0.2714	1.3017	0.0578	0.0462	0.0124	0.0329	-0.9089	-0.4008
-4	0.0249	0.0660	0.1567	0.2649	-0.1385	-0.6641	-0.0806	-0.0553	0.2562	0.6779	-0.6526	-0.2467
-3	-0.0691	-0.1829	0.0875	0.1295	0.1401	0.6720	0.0595	0.0356	-0.4374	-1.1573	-1.0901	-0.3605
-2	-0.0498	-0.1318	0.0377	0.0496	-0.3743	-1.7952	-0.3149	-0.1678	-0.1690	-0.4473	-1.2591	-0.3701
-1	-0.1629	-0.4311	-0.1252	-0.1482	-0.3135	-1.5034	-0.6284	-0.3013	0.3183	0.8422	-0.9408	-0.2489
0	-0.0954	-0.2524	-0.0954	-1.1290	-0.2434	-1.1675	-0.2434	-1.1675	-0.1397	-0.3695	-0.1397	-0.3695
+1	0.0692	0.1831	-0.0262	-0.1550	0.1472	0.7058	-0.0963	-0.2308	1.3292	3.5167	1.1895	1.5736
+2	0.0862	0.2282	0.0862	1.0203	0.1702	0.8162	0.1702	0.8162	-1.8663	**-4.9378**	-1.8663	**-4.9378**
+3	-0.0335	-0.0887	0.0527	0.3118	0.1268	0.6079	0.2969	0.7121	0.1187	0.3141	-1.7476	-2.3118
+4	-0.1648	-0.4361	-0.1121	-0.4422	-0.3543	-1.6991	-0.0573	-0.0917	0.3865	1.0225	-1.3611	-1.2004
+5	0.1310	0.3465	0.0189	0.0558	0.0330	0.1582	-0.0244	-0.0292	0.2485	0.6574	-1.1126	-0.7359
+6	0.0061	0.0162	0.0250	0.0591	-0.3500	-1.6785	-0.3744	-0.3591	-0.0846	-0.2239	-1.1972	-0.6335
+7	-0.1049	-0.2775	-0.0799	-0.1576	0.2708	1.2986	-0.1036	-0.0828	-0.2468	-0.6530	-14440	-0.6368
+8	-0.1788	-0.4730	-0.2587	-0.4373	-0.4176	-2.0025	-0.5211	-0.3570	0.3056	0.8085	-1.1384	-0.4303
+9	0.1360	0.3599	-0.1227	-0.1814	-0.0104	-0.0501	-0.5316	-0.3187	-0.6017	-1.5920	-1.7402	-0.5755
+10	-0.1180	-0.3122	-0.2407	-0.3164	0.2604	1.2487	-0.2712	-0.1445	-0.0079	-0.0209	-1.7480	-0.5139
+11	0.0170	0.0449	-0.2237	-0.2647	-0.0145	-0.0695	-0.2857	-0.1370	0.0057	0.0150	-1.7424	-0.4610
+12	0.0641	0.1697	-0.1596	-0.1716	-0.0679	-0.3257	-0.3536	-0.1542	0.1344	0.3555	-1.6080	-0.3868
+13	-0.0043	-0.0114	-0.1639	-0.1616	0.2537	1.2166	-0.0999	-0.0399	-0.0315	-0.0834	-1.6395	-0.3615
+14	-0.0988	-0.2615	-0.2627	-0.2391	0.1998	0.9584	0.0999	0.0369	0.4749	1.2565	-1.1646	-0.2370
+15	0.2020	0.5345	-0.0607	-0.0513	0.2558	1.2269	0.3558	0.1219	-0.7236	-1.9145	-1.8882	-0.3568

Dashed lines demarcate the anticipation window, event window, and post-event windows. AR indicates average abnormal returns, CAR indicates cumulative average abnormal returns, t indicates the value of the test-statistic. Positive - Standard indicates standard approvals defined as NDA 'type 1' and review classification 'Standard'. CAR for the anticipation window are calculated starting at day -10, starting at day 0, and starting at day +2 for the anticipation, event, and post-event window respectively. Dotted underlined values are significant at the 10% level, underlined values at the 5% level, and **underlined bold** values at the 1% level. Critical values were calculated using the normal distribution except for the negative announcements where the t distribution was used due to the low number of observations. All critical values are two-tailed.

6.2.4. EMEA

NASDAQ and NYSE Assets have a positive stock price anticipation prior to the actual EMEA announcement, largely driven by the stock price response following the CHMP Opinion announcement. A significant daily abnormal return is found for both NASDAQ ($p < 0.0001$) and NYSE ($p = 0.0385$) listed companies at day -48, the trading day corresponding approximately with CHMP Opinion announcement day. In the entire 60 day anticipation window, there are both significant positive and negative abnormal returns, but none resulting in significant cumulative abnormal returns (Table 7). NYSE listed companies have 10 significant abnormal daily returns in the entire anticipation window, however not resulting in significant cumulative returns as there is an equal number of significant positive and negative returns.

Table 7: Overview of the event study statistics of EMEA positive NASDAQ and NYSE Assets calculated using the Fama-French model and the NASDAQ Biotech Index and NYSE Pharmaceutical Index respectively.

Day	Positive - NASDAQ				Positive - NYSE			
	Daily		Cumulative		Daily		Cumulative	
	AR	t	CAR	t	AR	t	CAR	t
-10	0.1745	0.6978	0.1745	0.6978	-0,1880	-2.2404	-0.1880	-2.2404
-9	0.2194	0.8775	0.3938	0.7877	0,0579	0.6901	-0.1301	-0.7752
-8	-0.2858	-1.1430	0.1081	0.1441	0,1349	1.6075	0.0048	0.0190
-7	-0.1279	-0.5115	-0.0198	-0.0198	-0,1221	-1.4550	-0.1173	-0.3495
-6	-0.3109	-1.2436	-0.3307	-0.2646	-0,2042	-2.4328	-0.3215	-0.7661
-5	-0.1720	-0.6882	-0.5028	-0.3352	-0,2045	-2.4369	-0.5260	-1.0446
-4	-0.9014	**-3.6056**	-1.4042	-0.8024	0,2127	2.5348	-0.3133	-0.5333
-3	0.6109	2.4435	-0.7933	-0.3966	-0,1099	-1.3102	-0.4232	-0.6304
-2	0.0939	0.3756	-0.6994	-0.3108	-0,0484	-0.5770	-0.4716	-0.6244
-1	0.2155	0.8620	-0.4839	-0.1936	0,0596	0.7101	-0.4120	-0.4910
0	-0.5443	-2.1772	-0.5443	-2.1772	-0,0838	-0.9991	-0.0838	-0.9991
+1	-0.0184	-0.0736	-0.5627	-1.1254	-0,1496	-1.7827	-0.2334	-1.3909
+2	-0.4279	-1.7115	-0.4279	-1.7115	-0,0135	-0.1610	-0.0135	-0.1610
+3	-0.0655	-0.2622	-0.4934	-0.9869	-0,1256	-1.4964	-0.1391	-0.8287
+4	0.8430	**3.3721**	0.3496	0.4661	-0,0280	-0.3332	-0.1670	-0.6635
+5	0.5572	2.2288	0.9068	0.9068	-0,0740	-0.8823	-0.2411	-0.7182
+6	-0.4311	-1.7243	0.4757	0.3806	0,1186	1.4134	-0.1225	-0.2919
+7	0.0174	0.0696	0.4931	0.3287	-0,2175	**-2.5913**	-0.3399	-0.6751
+8	0.2323	0.9292	0.7254	0.4145	-0,1853	-2.2083	-0.5253	-0.8942
+9	-0.1856	-0.7425	0.5398	0.2699	0,0131	0.1565	-0.5121	-0.7628
+10	0.4547	1.8188	0.9945	0.4420	-0,0136	-0.1615	-0.5257	-0.6960
+11	-0.2532	-1.0129	0.7412	0.2965	-0,0269	-0.3209	-0.5526	-0.6585
+12	0.1007	0.4029	0.8420	0.3062	-0,2249	**-2.6800**	-0.7775	-0.8423
+13	0.1322	0.5286	0.9741	0.3247	-0,0774	-0.9226	-0.8549	-0.8490
+14	0.1506	0.6023	1.1247	0.3461	-0,0066	-0.0783	-0.8615	-0.7897
+15	0.4752	1.9008	1.5999	0.4571	0,0061	0.0727	-0.8554	-0.7281

Dashed lines demarcate the anticipation window, event window, and post-event windows. AR indicates average abnormal returns, CAR indicates cumulative average abnormal returns, t indicates the value of the test-statistic. CAR for the anticipation window are calculated starting at day -10, starting at day 0, and starting at day +2 for the anticipation, event, and post-event window respectively. Dotted underlined values are significant at the 10% level, underlined values at the 5% level, and **underlined bold** values at the 1% level. Critical values were calculated using the normal distribution except for the NASDAQ Assets where the t distribution was used due to the low number of observations. All critical values are two-tailed.

Both EMEA positive NASDAQ and NYSE Assets exhibit significant negative abnormal returns in the announcement event window. These results are quite puzzling and can only be explained by anecdotal trading strategies such as 'buy the rumour, sell the news'. The stock price in the post-announcement window shows both significant positive and negative abnormal returns, but no significant cumulative returns (Table 7).

In general, there appears to be no significant 'logical' response of NASDAQ and NYSE listed companies to official EMEA announcements. This could be explained by two different reasons. First, the sample under study contains only NYSE and NASDAQ listed companies. It is not unreasonable to assume investors of such companies are more focussed on the decisions made by the American FDA than by the European EMEA. Second, the CHMP Opinion seems to be a more important decision than the official announcement made later by the EMEA. However, I did not have access to an extensive dataset of CHMP Opinion dates as only the official final EMEA announcement dates are publicly available. Further research could focus on EMEA Opinion announcement dates, rather than final EMEA announcements dates.

7. BENEFITING FROM THE INSIGHTS – TRADING SIMULATIONS

I simulated several trading strategies to test whether profitable trading strategies can be devised using the insights obtained with respect to the stock price anticipation, immediate stock price response, and post-announcement stock price behaviour. The simulated trading strategies were relatively simple as a stock was always bought or sold a fixed number of days prior to or past the announcement date. The performance of the trading strategies was benchmarked against index tracking investment returns.

The results pointing to possible profitable trading strategies are limited to FDA positive and FDA negative NASDAQ related announcements. As a consequence, only these announcements events are investigated for profitable trading strategies.

7.1. METHODOLOGY

Given a specific FDA announcement event, a virtual trading agent was given a 50% choice to either use the event or not use the event as a trading opportunity. This simulates a real trading environment of a retail investor which can only use a certain percentage of trading opportunities. Furthermore, this allows for some variability in the returns which enables additional statistics to be determined rather than just the average returns of trading all the announcement events. Once the virtual trading agent had decided to initiate a trading position given the announcement event, the agent was allowed to invest a maximum of 50% of the available funds in case of a 'long' investmet. In case of a short investment, the trading agent was obliged to keep 100% of the short investment as margin; the agent could have a maximum of 50% of the available funds as margin for a single short investment.

Furthermore, it is assumed the stocks were liquid enough to allow the trades to take place and that the trades did not influence the stock behaviour due to perfect competition. Stocks were bought and sold at the closing price and a 1% transaction cost was deducted from the invested funds each time a transaction took place. Uninvested funds (excess liquidity) could be invested in the ^NBI or ^IXIC. Indexes were purchased at the day high and sold at the day low price; this 'spread crossing' acts as the transaction fee.

Several scenarios were analysed in which the trading agent could buy or sell a stock on a fixed number of days prior to or past the announcement date. The trading agent was allowed to take both long (i.e. buy in the hope to sell at a higher price) and short (i.e. sell in the hope to buy back a lower price) positions.

A virtual trading portfolio was initiated with $10,000 at 1 November 2007. Holding period returns according to equation (1) were calculated at 1 September 2012. For each of the different scenarios, 1,000 simulations were performed of which the HPR, the average HPR, variance of the HPR, excess returns and an Excess Performance was calculated.

The Excess Performance (EP) index, similar to the Sharpe ratio, was calculated as following:

$$EP = \frac{\overline{R_{sim}} - R_{index}}{\sigma_{R_{sim}-R_{index}}} \tag{35}$$

where $\overline{R_{sim}}$ is the simulated holding period return averaged over all simulations, R_{index} the holding period return of either the ^NBI or ^IXIC, and $\sigma_{R_{sim}-R_{index}}$ the standard error of the excess returns.

7.2. RESULTS AND DISCUSSION

7.2.1. INDEX RETURNS

Holding period returns were calculated for the entire period (1 November 2007 – 1 September 2012) for both the ^NBI and ^IXIC. The holding period return was 61.69% for the ^NBI and 12.76% for the ^IXIC.

7.2.2. ANTICIPATION WINDOW

Buying NASDAQ Assets 60 days prior to the announcement date and selling them 5 days prior to the announcement date results in an average HPR of 182.68%, clearly outperforming both the ^NBI and ^IXIC (Table 8). The distribution of HPRs is not symmetrical; returns larger than 600% could be obtained using this trading strategy. This trading strategy never results in negative returns and almost always performs better than the HPR obtained by investing in ^NBI or ^IXIC (Figure 12). Consequently, selling NASDAQ Assets 60 days prior to the announcement date and buying them back 5 days prior to the announcement date results in a loss larger than 99 % (Table 9).

Investing the excess liquidity in an index lowers the variance of the obtained returns, but at a cost of a lower average return. The EP index either changes slightly in a positive direction or changes a lot in a negative direction. Most of the time, most of the money is invested, making the incurred transaction costs responsible for the negative impact of this investment strategy. For example the window between 60 and 5 trading days prior the announcement date is 55 trading days long and there are 91 FDA events which are traded in these simulations; periods of excess liquidity are very short and the amounts of excess liquidity very small. However, the returns of the simulations using liquidity investment depend largely on the cost factor applied to step in and out of index investments. When costs are doubled per

opening/closing trade, the average return drops from 179.47% to 141.06%. Although still significantly outperforming both the ^NBI and ^IXIC, a significant reduction in returns is observed.

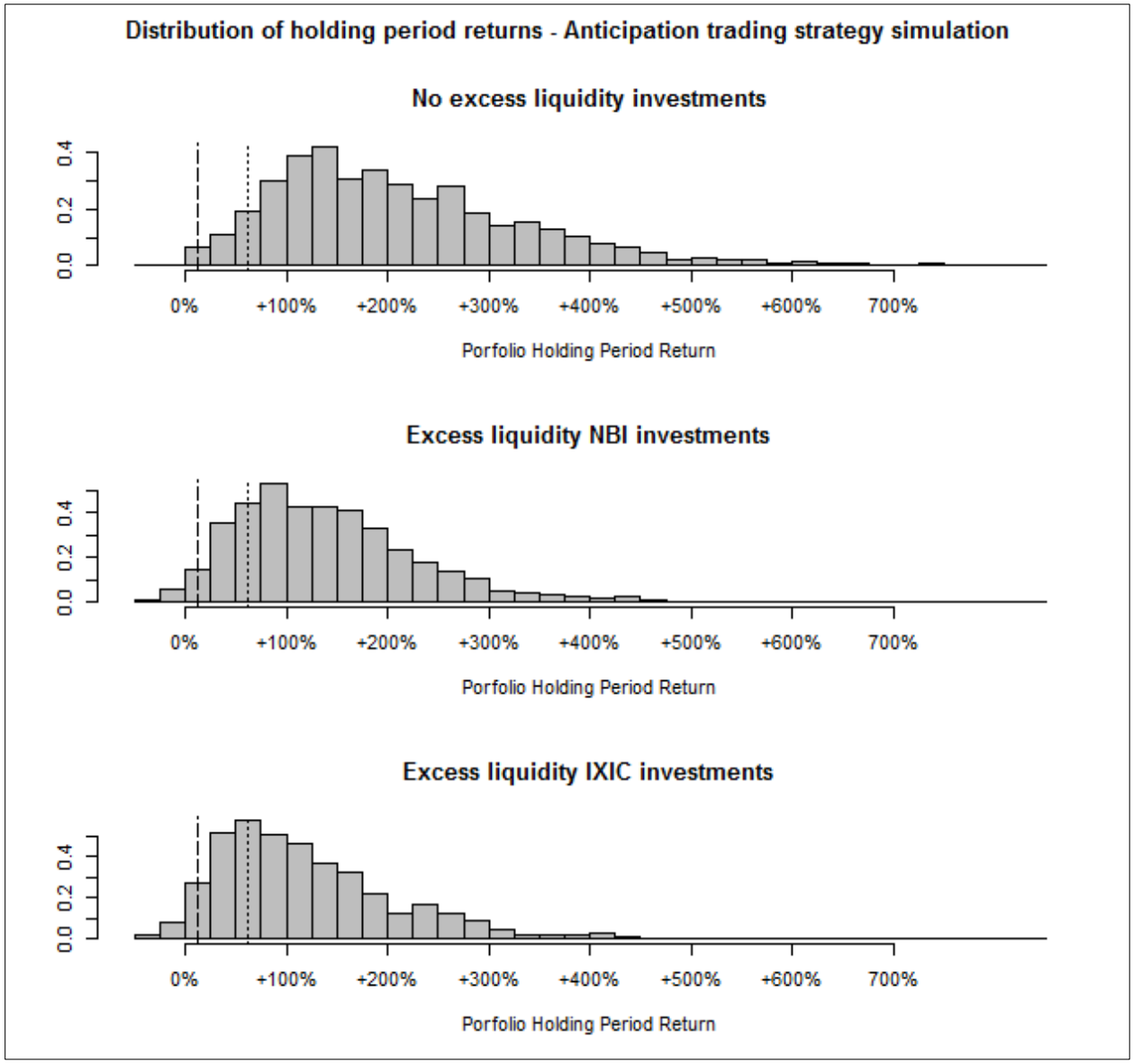

Figure 12: Distribution of simulated trading returns using an anctipation trading strategy where NASDAQ listed stocks are purchased 60 days prior to an FDA announcement and sold 5 days prior to an FDA announcement. The short dashed line indicates the holding period return of the ^NBI, the long dashed line the holding period return ofthe ^IXIC.

7.2.3. ANNOUNCEMENT EVENT

A strategy where an investor does not know whether the FDA announcement will be positive or negative cannot earn money with either a long or short strategy when initiating the trading position 60 days prior to the announcement date. A strategy where trading positions are initiated 60 days prior to the announcement date will be able to capture the stock price increase in the entire anticipation

window. However, the large stock price reaction (both negative or positive) will wipe out a large portion of the invested funds. Once a large majority of the money is wiped out by a bad investment, it is difficult to earn back a sizeable capital (see Table 8 for long strategies and Table 9 for short strategies). This means an investor cannot earn money by blindly 'placing bets', unless he has some method to determine the actual outcome of the announcements in advance.

A strategy where an investor buys 5 days prior to the announcement date will not be profitable as the anticipation is completely priced in already. However, as was noticed before (Sharma and Lacey 2004) and is evident from the research conducted in this thesis, responses to FDA announcements are highly assymetric; i.e. negative announcements have a far more negative impact than the positive impact of positive news. Bearing this in mind, a profitable trading strategy can be found in going short prior to all announcements (-5 days) and closing the position immediately after the announcement (+2 days). This strategy results in an average HPR of 172 %. However, as this strategy relies on the ratio of the number of positive and negative FDA announcements, which is unknown *ex-ante*, this remains a risky strategy. A situation where only positive FDA announcements are used in this shorting strategy results in losses of 69.40%.

Table 8: Summary statistics of trading simulations using different 'long' strategies.

Buy/Sell	**Liq.**	$\bar{R}$	$\bar{R} - R_{NBI}$	$\bar{R} - R_{IXIC}$	σ_R^2	EP_{NBI}	EP_{IXIC}
[-60; -5]**	None	182.68%	120.58%	168.59%	130.26%	1.0565	1.4860
	NBI	179.47%	117.78%	166.80%	119.89%	1.07842	1.5272
	IXIC	145.09%	83.408%	132.43%	110.66%	0.7929	1.2588
[-60; +2]	None	-4.54%	-66.23%	-17.21%	48.59%	-0.9500	-0.2469
	NBI	-10.60%	-72.29%	-23.70%	37.50%	-1.1804	-0.3799
	IXIC	-19.52%	-81.21%	-32.19%	45.59%	-1.2444	-0.4932
[-60; +15]	None	-0.63%	-62.32%	-13.30%	40.34%	-0.9812	-0.2094
	NBI	-1.81%	-63.50%	-14.48%	34.98%	-1.0736	-0.2448
	IXIC	-16,15%	-77.84%	-28.82%	25.83%	-1.5314	-0.5669
[-5; +2]	None	-89.68%	-151.37%	-102.35%	0.13%	-41.8802	-28.3182
	NBI	-90.61%	-152.30%	-103.28%	0.18%	-22.8665	-15.3003
	IXIC	-89.20%	-150.89%	-101.87%	0.17%	-36.9287	-24.9319
[+1; +15]	None	-84.55%	-146.23%	-97.22%	0.29%	-27.201	-18.0831
	NBI	-75.05%	-138.56%	-89.55%	0.69%	-16.6946	-10.7888
	IXIC	-83.74%	-145.43%	-96.41%	0.30%	-26.7509	-17.7343

* Indicate profitable strategies, ** indicates profitable strategies outperforming index tracking investments.
Liq. Indicates wherein the excess liquidy funds were invested.

Table 9: Summary statistics of trading simulations using different 'short' strategies.

Sell/Buy	Liq.	$\overline{R}$	$\overline{R} - R_{NBI}$	$\overline{R} - R_{IXIC}$	σ_R^2	EP_{NBI}	EP_{IXIC}
[-60, -5]	None	-99.12%	-160.08%	-111.779%	4.15%	-7.8943	-5.4879
[-60; +2]	None	-99.39%	-161.07%	-112.06%	40.07%	-2.5446	-1.7702
[-60; +15]	None	-99.45%	-161.13%	-112.12%	46.27%	-2.3689	-1.6483
[-5, +2]N**	None	415.16%	353.47%	402.49%	486.28%	1.6029	1.8252
[-5; +2]P	None	-69.40%	-131.09%	-82.07%	3.15%	-7.3889	-4.6259
[-5; +2]**	None	172.26%	110.57%	159.59%	355.15%	0.5867	0.8468
[+1; +15]N*	None	60.93%	-0.76%	48.26%	14.84%	-0.0196	1.2531
[+1; +15]P*	None	8.99%	-52.69%	-3.67%	9.31%	-1.7262	-0.1204
[+1, +15]**	None	68.29%	6.61%	55.62%	35.21%	0.1113	0.9374

P and N correspond to positive and negative announcements respectively.

* Indicates profitable strategies, ** indicates profitable strategies outperforming index tracking investments.

Liq. Indicates wherein the excess liquidy funds were invested.

7.2.4. POST-ANNOUNCEMENT

Anecdotal evidence suggests many retail investors are frustrated with an apparent rational trading strategy. Relatively risk-averse retail investors are attracted by the high returns of small biotech firms induced by positive regulatory decisions. However, in an effort to avoid the risk imposed by the regulatory decision, many investors purchase after the announcement. However, in previous sections it has been demonstrated there are significant negative returns in the trading days following the announcement for NASDAQ Assets.

Indeed, a trading strategy where stocks are purchased 2 days after the announcement has been made and sold 15 days after the announcement results in an average HPR of -84.55% with a variance of 0.29%, a certain but losing strategy (Table 8). However, a short strategy where stocks are shorted immediately after the announcement (day +1) and bought back a short period later (day +15) results in an average HPR of 60.93%. The result is more outspoken when this strategy is only applied to negative announcements. The strategy is profitable and outperforming an ^IXIC investment, but not an ^NBI investment though (Table 9).

7.3. CONCLUDING REMARKS

This section demonstrated the insights obtained in this thesis can indeed result in profitable trading strategies when considering FDA positive and negative NASDAQ Assets. A strategy where an investors goes long 60 days prior the announcement date and closes the position 5 days prior to the announcement date results in average returns outperforming index tracking investments. So does a strategy where an investor goes short 5 days prior to the announcement date and closes the position 2 days past the announcement date. Furthermore, a strategy where an investor goes short immediately

after the announcement and closes the position 15 days later, results in positive returns which are not larger than index tracking investments.

Further research could focus on more advanced trading strategies combining the insights from this section. Furthermore, analyses could be performed, similar to the analyses carried out by Sharpe in his seminal market timing parper, where an investor has the ability to guess a certain percentage of outcomes correctly (Sharpe 1975). This way, a relationship could be determined between the profitability of certain trading strategies and the ability to 'predict' regulatory announcements.

8. CONCLUSIONS AND FUTURE PERSPECTIVES

The stock price response of NASDAQ and NYSE listed companies to 403 regulatory decisions by the US Food and Drug Administration (FDA) and European Medicine Agency (EMEA) between January 2008 and September 2012 was investigated in this study. There are clear differences between stock price responses to FDA and EMEA decisions and between NASDAQ and NYSE listed companies. The stock price of NASDAQ listed companies shows a significant positive anticipation over a 60 day window leading up to both positive and negative FDA announcements. Trading strategies exploiting this positive anticipation result in significant excess positive returns. In case of negative FDA announcements, NASDAQ listed companies show a significant short-term decline prior to the actual announcement. This is probably the result of particular investors selling the stock in anticipation of the actual negative announcement, possibly having non-public information regarding the decision.

NASDAQ listed companies show significant instantaneous stock price responses on the day of the FDA announcement. However, responses are clearly asymetrical; negative news comes more as a shock than positive news. Overall, managers should be very careful at considering the signals they send to the markets before final approvals since negative surprises are heavenly sanctioned by financial markets. Again, trading strategies exploiting this asymetry result in significant excess returns.

The stock price of NASDAQ listed companies do not respond efficiently to FDA announcements; investors seem to have been overoptimistic immediately following an announcement. Both following positive and negative FDA announcements, the stock price of NASDAQ listed companies show significant negative returns. The stock price of NYSE listed companies show some positive anticipation leading up to positive FDA announcements. However, there is no significant response on the announcement day or the days following the announcement.

These findings only partially partially correspond with earlier results. However, the period under consideration (2008-2012) was atypical and contained both periods of high and low volatility and high and low stock investor confidence. Further research will need to be carried out to verify whether these observed results are typical for the period under consideration or are also present in future time periods. Furthermore, futurer research could also focus on the different subperiods in the 2008-2012 period where periods of global market enthusiasm were followed by periods of severe global market pessimism.

Both NASDAQ and NYSE listed companies do not seem to systematically anticipate or respond to positive EMEA announcements. These differences between the response to FDA and EMEA announcements is striking and could be the subject of more detailed future research. However, this study focussed solely on companies listed on American exchanges, probably focussing more on the American market. Companies listed on European exchanges might be more responsive to European regulatory announcements than American companies or to American regulatory announcements.

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APPENDICES

Appendix 1: Overview of the Big Pharma (BP) companies subsample used in different analyses.

Name	Ticker	Exchange	Revenue	Employees
Eli Lilly and Co.	LLY	NYSE	$ 24.29 bln	38,350 (2010)
Pfizer	PFE	NYSE	$ 67.42 bln	103,700
Merck and Co. AG	MRK	NYSE	$ 48.05 bln	86,000
GlaxoSmithKline plc	GSK	NYSE	£ 26.43 bln (2012)	97,389
Abbott Laboratories	ABT	NYSE	$ 38.85 bln	91,000
Bristol Myers Squibb Co.	BMY	NYSE	$ 21.20 bln	27,000
Johnson & Johnson	JNJ	NYSE	$ 65.03 bln (2012)	117,900 (2012)
Novartis AG	NVS	NYSE	$ 58.57 bln	119,418 (2010)
Sanofi SA	SNY	NYSE	€ 33.38 bln	113,719

Numbers are for end 2011 unless mentioned otherwise. [Source: Financial reports and company websites]

Appendix 2: Overview of the FDA announcements

Positive FDA announcements

A list of all the positive FDA announcements studied in this thesis is available online from this URL: http://www.joachimdeschrijver.be/thesisEW2013/Database/DatabaseDump_FDA_approvals.xls.

This list contains the following fields:

Table field	Explanation	Example value
Date	Date on which the FDA announced the decision.	10/01/2008
Drug_name	Commercial name of the drug.	Alvesco
Duplicate	Boolean for duplicate entries [0-1].	0
Active_ingredient	Scientific name of the drug.	Ciclesonide
FDA_app_nr	FDA application Nr.	NDA #021658
NDA_type	NDA application type [1-6].	3
Review_classification	Priority of the application. Standard [S] or Priority [P].	S
Company	Name of the company which developed the drug.	Nycomed GMBH
Type	Company type. Public or Private.	Public
Xchange	Xchange on which the public company is listed.	TSE
Ticker	Ticker of the public company.	4502

Negative FDA announcements

A list of all the negative FDA announcements studied in this thesis is available online from this URL: http://www.joachimdeschrijver.be/thesisEW2013/Database/DatabaseDump_FDA_refusals.xls.

This list contains the following fields:

Table field	Explanation	Example value
Date	Tentative date on which the FDA announced the decision.	18/02/2008
Drug_name	Commercial name of the drug.	Zyprexa
Duplicate	Boolean for duplicate entries [0-1].	0
Company	Name of the company which developed the drug.	Lilly
Type	Company type. Public or Private.	Public
Xchange	Xchange on which the public company is listed.	NYSE
Ticker	Ticker of the public company.	LLY

Appendix 3: Overview of the EMEA announcements

A list of all the EMEA announcements studied in this thesis is available online from this URL: http://www.joachimdeschrijver.be/thesisEW2013/Database/DatabaseDump_EMEA_all.xls.

This list contains the following fields:

Table field	Explanation	Example value
Medicine Name	Commercial name of the drug	Tesavel
Product Number	EMEA number of the drug application	EMEA/H/C/000910
Active Substance	Scientific name of the drug	sitagliptin
Common name	Common name of the drug	sitagliptin
ATC code	ATC code designation	L04AA06
Status	Status of the application (authorised/refused)	Authorised
Revision numer	Number of revision	6
Authorization date	Date of decision	20/05/2008
Condition Approval	Boolean for conditional approval [0-1]	0
Exceptional	Boolean for exceptional circumstances [0-1]	0
Is Orphan	Boolean for orphan medicine [0-1]	0
Is Generic	Boolean for generic medicine [0-1]	0
Is Biosimilar	Boolean for biosimiliar medicine [0-1]	0
Duplicate	Boolean for duplicate entries [0-1].	0
Company	Name of the company which developed the drug.	Lilly
Type	Company type. Public or Private.	Public
Xchange	Xchange on which the public company is listed.	NYSE
Ticker	Ticker of the public company.	LLY

Appendix 4: Descriptive statistics of the companies of which the FDA approved or refused products between January 2008 and September 2012.

FDA approvals

Type	Trading place	Count	Percentage
Private		130	29.6 %
Public		308	70.4 %
NYSE	New York Stock Exchange, USA	153	49.7 %
NASDAQ	NASDAQ, USA	60	19.5 %
NSE	National Stock Exchange, India	24	7.8 %
TSE	Tokyo Stock Exchange, Japan	23	7.5 %
LSE	London Stock Exchange, UK	11	3.6 %
FWB	Frankfurt Stock Exchange, Germany	7	2.3 %
OMX STO	Stockholm Stock Exchange, Sweden	5	1.6 %
EBR	Euronext Brussels, Belgium	5	1.6 %
OTC	Over-The-Counter Market, USA	4	1.3 %
SIX	SIX Swiss Exchange, Switzerland	4	1.3 %
TSX	Toronto Stock Exchange, Canada	4	1.3 %
OMX CPH	Copenhagen Stock Exchange, Denmark	3	1.0 %
ASX	Australian Stock Exchange	2	1.0 %
ERP	Euronext Paris, France	1	0.5 %
BI MI	Borsa Italia Milan, Italy	1	0.5 %
STU	Stuttgart Stock Exchange, Germany	1	0.5 %
Grand total		438	100 %

FDA refusals

Type	Trading place	Count	Percentage
Private		8	11.6 %
Public		61	88.4 %
NASDAQ	New York Stock Exchange, USA	44	72.1 %
NYSE	NASDAQ, USA	8	11.6 %
AMEX	National Stock Exchange, India	3	4.9 %
OTC	Over-The-Counter Market, USA	3	4.9 %
ASX	Australian Stock Exchange	1	1.6 %
FWB	Frankfurt Stock Exchange, Germany	1	1.6 %
ERP	Euronext Paris, France	1	1.6 %
Grand total		69	100 %

Appendix 5: Descriptive statistics of the companies of which the EMEA approved or refused products between January 2008 and September 2012.

EMA approvals

Type	Trading place	Count	Percentage
Private		69	21.2 %
Public		257	78.8 %
NYSE	New York Stock Exchange, USA	157	61.1 %
TSE	Tokyo Stock Exchange, Japan	21	8.2 %
NASDAQ	NASDAQ, USA	19	7.4 %
LJSE	Ljubljanska borza, Slovenia	17	6.6 %
LSE	London Stock Exchange, UK	7	2.7 %
NSE	National Stock Exchange, India	6	2.3 %
SIX	SIX Swiss Exchange, Switzerland	5	1.9 %
AMS	Euronext Amsterdam, The Netherlands	5	1.9 %
EBR	Euronext Brussels, Belgium	4	1.6 %
ASX	Australian Stock Exchange	3	1.2 %
OMX HEL	Helsinki Stock Exchange, Finland	3	1.2 %
STU	Stuttgart Stock Exchange, Germany	2	0.8 %
OMX STO	Stockholm Stock Exchange, Sweden	2	0.8 %
BI MI	Borsa Italia Milan, Italy	2	0.8 %
BME	Bolsa de Madrid, Spain	2	0.8 %
FWB	Frankfurt Stock Exchange, Germany	1	0.4 %
VI	Vienna Stock Exchange, Austria	1	0.4 %
Grand total		326	100%

EMA refusals

Type	Trading place	Count	Percentage
Private		3	25.0 %
Public		9	75.0 %
NYSE	New York Stock Exchange, USA	4	33.3 %
NASDAQ	NASDAQ, USA	3	25.0 %
AMS	Euronext Amsterdam, The Netherlands	1	8.3 %
EBR	Euronext Brussels, Belgium	1	8.3 %
Grand total		12	100 %

Appendix 6: Overview of the analysis framework

A large quantity of data needed to be analysed and aggregated; this for different agencies (FDA and EMEA), different exchanges (NASDAQ and NYSE), and different announcements (positive and negative). To ensure an identical analysis methodology over all different datasets, avoid human errors, speed up analyses, and automate analyses in general, a computational analysis framework was developed in Perl (Schwartz and Phoenix 2003; Cozens 2005; Foy 2007) and R which allows each of these goals to be met.

The analysis framework can be divided into two main parts: 1) the event part and 2) the prices part, as shown in the image below. Both the daily price information of all the stocks of interest and the FDA and EMEA announcements of interest are stored in a relational MySQL database. Using the `query_events` functionality, a user can fill an `EventBackpack` object with `SingleDecisionEvent` objects. For example, a searching query can be defined as agency = 'FDA', announcement type = 'authorised', and trading exchange = 'NASDAQ'. Using these parameters, the `EventBackpack` will be filled with all the announcement events (=`SingleDecisionEvent` objects) satisfying these conditions.

Each of these `SingleDecisionEvent` objects can then be converted to an `EventDayChain` object using the pricing information which is queried from the price database through `SingleTradingDay` objects. Eventually, an `EventDayChain` object becomes an object which contains a series of pricing information in a user defined window around the actual announcement date. For example, a typical analysis script wants to retrieve stock price information from -60 trading days to -1 trading day in respect to the actual announcement day; and this only for companies listed on for example NASDAQ having products approved by the FDA . Using the data contained in a `SingleDecisionEvent` object, and specifying -60 to -1 days, pricing information will be automatically retrieved from the database and organised in such a way so that future analyses are straightforward (using the `retrieve_SingleTradingDays_around_window` functionality).

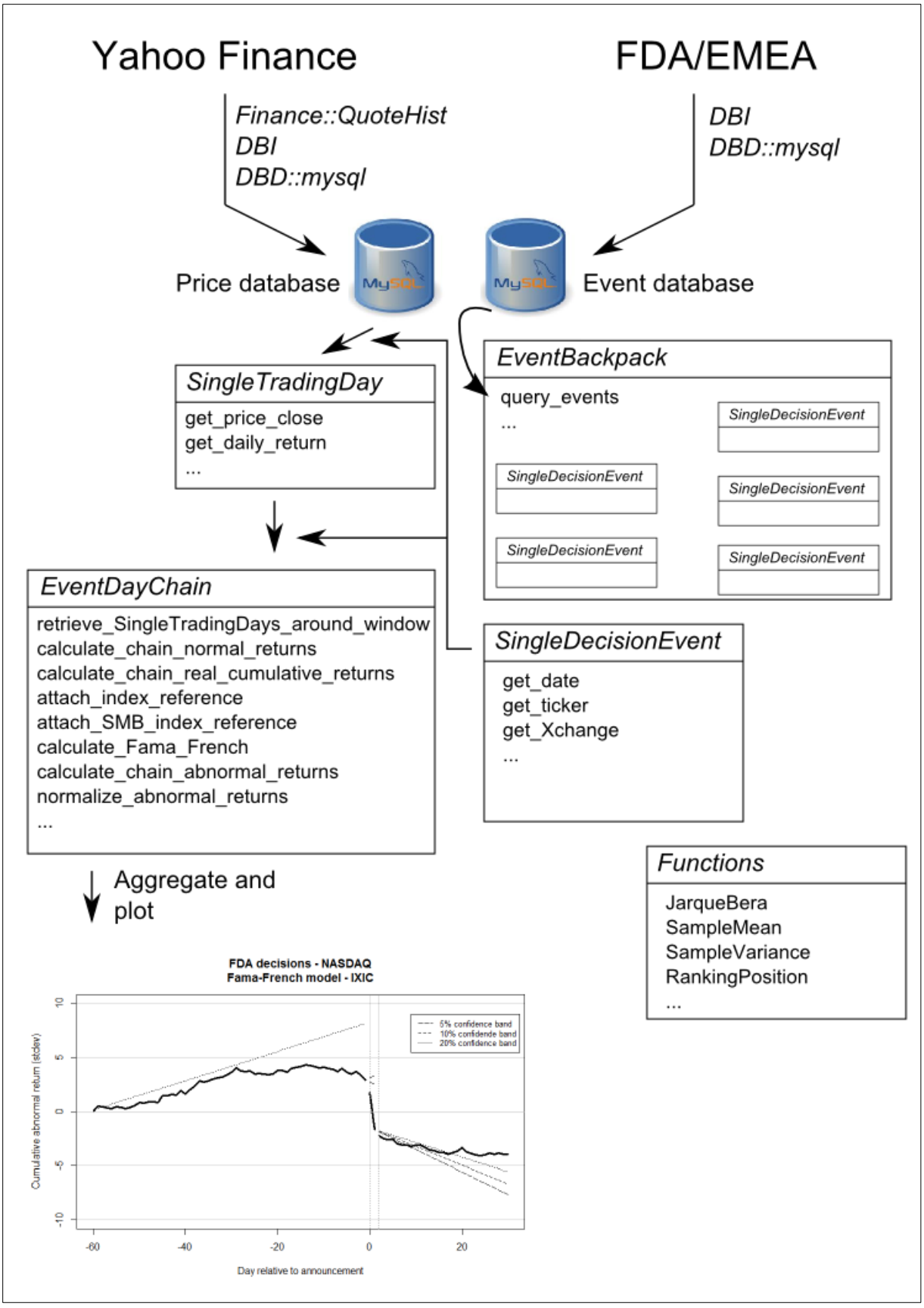
Once all data on a single announcement is stored in a single `EventDayChain` object, users can attach reference indexes using the `attach_index_reference` functionality. Again, all pricing information is automaticall retrieved from the database, checked for consistency with the stock price information, and prepared for future analyses. Once a reference is attached, the user can automatically regress observed returns on a number of explanatory variables such as for example index returns (i.e. calculate factor model coefficients) or Fama-French parameters. Once these regressions are carried out, the user

can retrieve the value of the coefficients, but also t-statistics or p-values to test significance. Once these coefficients are determined, normal returns, cumulative normal returns, abnormal returns, variance of returns, cumulative abnormal returns, normalized abnormal returns etc can easily be calculated. Important to note is that all these operations are carried out on the entire chain of prices (`EventDayChain` object). It is only a small step to aggregate the results over different events and come up with aggregated conclusions for an entire `EventBackpack` object. After the data has been exported, most figures in this thesis were generated using the statistical program R.

The analysis framework was completely custom built in Perl using a variety of existing small modules where applicable. Basic statistical features such as medians, variances, standard deviations were calculated using the Perl module `Statistics::Descriptive` and `Statistics::Basic`. Standard multiple (matrix based) ordinary least squares regressions were carried out using the Perl module `Statistics::Regression`. Simple regressions (e.g. the single-factor model) were carried out using the faster Perl modules `PDL` and `PDL::Stats`. Bartlett testing for equality of variances was carried out using `Statistics::Distributions::Bartlett` and Wilcoxon rank-sum testing using `Statistics::Test::WilcoxonRankSum`. Database interactions were performed using `DBI` and `DBD::mysql`. Debugging and error reporting are carried out using `Data::Dumper` and `Carp`. Many of the images were generated in R, where distribution were analysed using the `tseries` package (calculating skewness and JarqueBera coefficients) and the `e1071` package (distributional calculations).

It is interesting to note that as long as an index and stock ticker is available, together with a date of an event of interest, the length of the different windows, the model to be used in analyses (factor model or Fama-French), all the analyses can be carried out in approximately 20 lines of coding. These events can be any event of interest such as dividend pay days, earnings announcements, news announcements etc as long as a specific date is available.

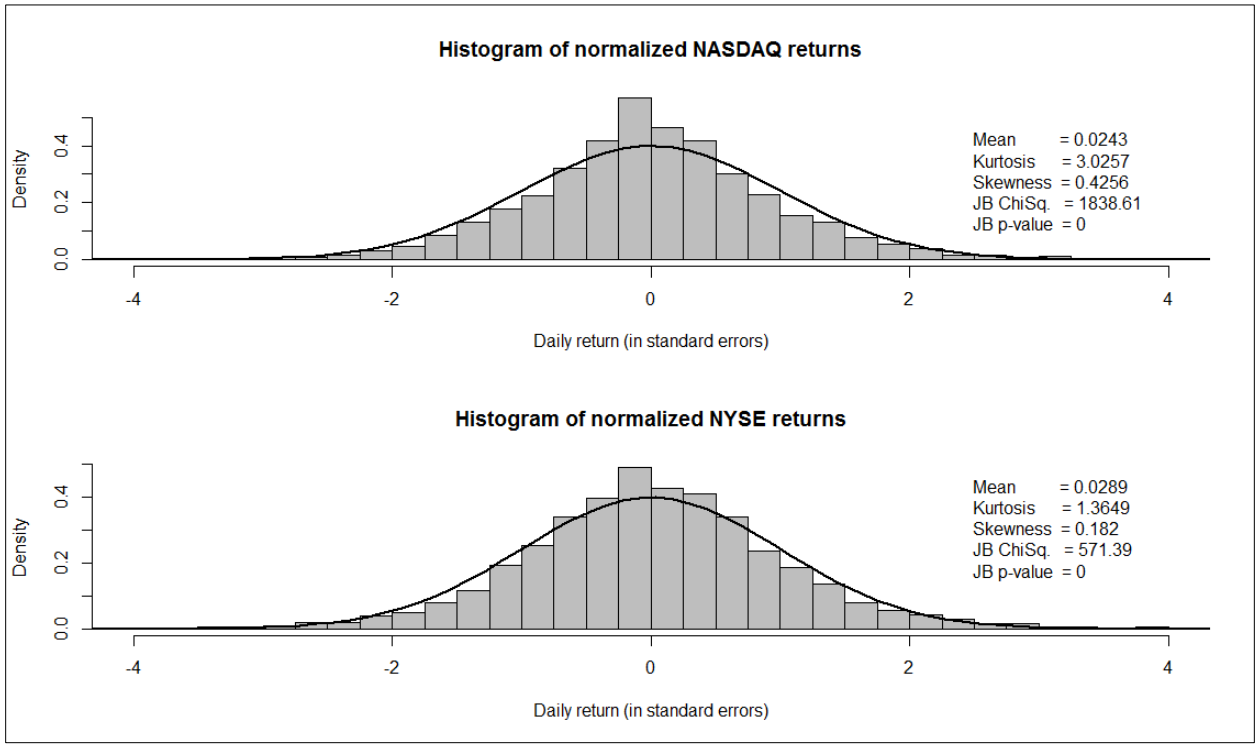
All the developed modules, scripts, and analysis pipelines are freely available online at http://www.joachimdeschrijver.be/thesisEW2013/scripts/.


Yahoo Finance
FDA/EMEA
Finance::QuoteHist
DBI
DBD::mysql
DBI
DBD::mysql
Price database
Event database
SingleTradingDay
get_price_close
get_daily_return
...
EventBackpack
query_events
...
SingleDecisionEvent
SingleDecisionEvent
SingleDecisionEvent
SingleDecisionEvent
SingleDecisionEvent
EventDayChain
retrieve_SingleTradingDays_around_window
calculate_chain_normal_returns
calculate_chain_real_cumulative_returns
attach_index_reference
attach_SMB_index_reference
calculate_Fama_French
calculate_chain_abnormal_returns
normalize_abnormal_returns
...
SingleDecisionEvent
get_date
get_ticker
get_Xchange
...
Functions
JarqueBera
SampleMean
SampleVariance
RankingPosition
...
Aggregate and plot
FDA decisions - NASDAQ
Fama-French model - IXIC
5% confidence band
10% confidende band
20% confidence band
Cumulative abnormal return (stdev)
Day relative to announcement

Appendix 7: Distribution of normalized daily NASDAQ and NYSE returns.

Daily stock price returns for all the companies included in the study were calculated for each trading day between 140 and 90 prior to the FDA or EMEA announcement date. Using these daily returns, an event specific sample standard deviation was calculated which was used to normalize these 50 daily returns. This set of 50 daily returns was calculated for each of the stocks associated with the 403 announcement events under study and then grouped per trading exchange.

The distribution of normalized NASDAQ returns was constructed using 5,500 normalized daily returns, the distribution of normalized NYSE returns was constructed using 14,650 normalized daily returns (as shown in the figure below). Both distributions are clearly non-normal as the means are not equal to 0, they are slightly skewed and heavily leptokurtic ("fat tails"), resulting in significant JarqueBera values for non-normality (p-values are twice 0). Also note that the black lines indicate a real normal distribution.



Appendix 8: 16 Members of the NYSE Pharmaceutical (DRG) index

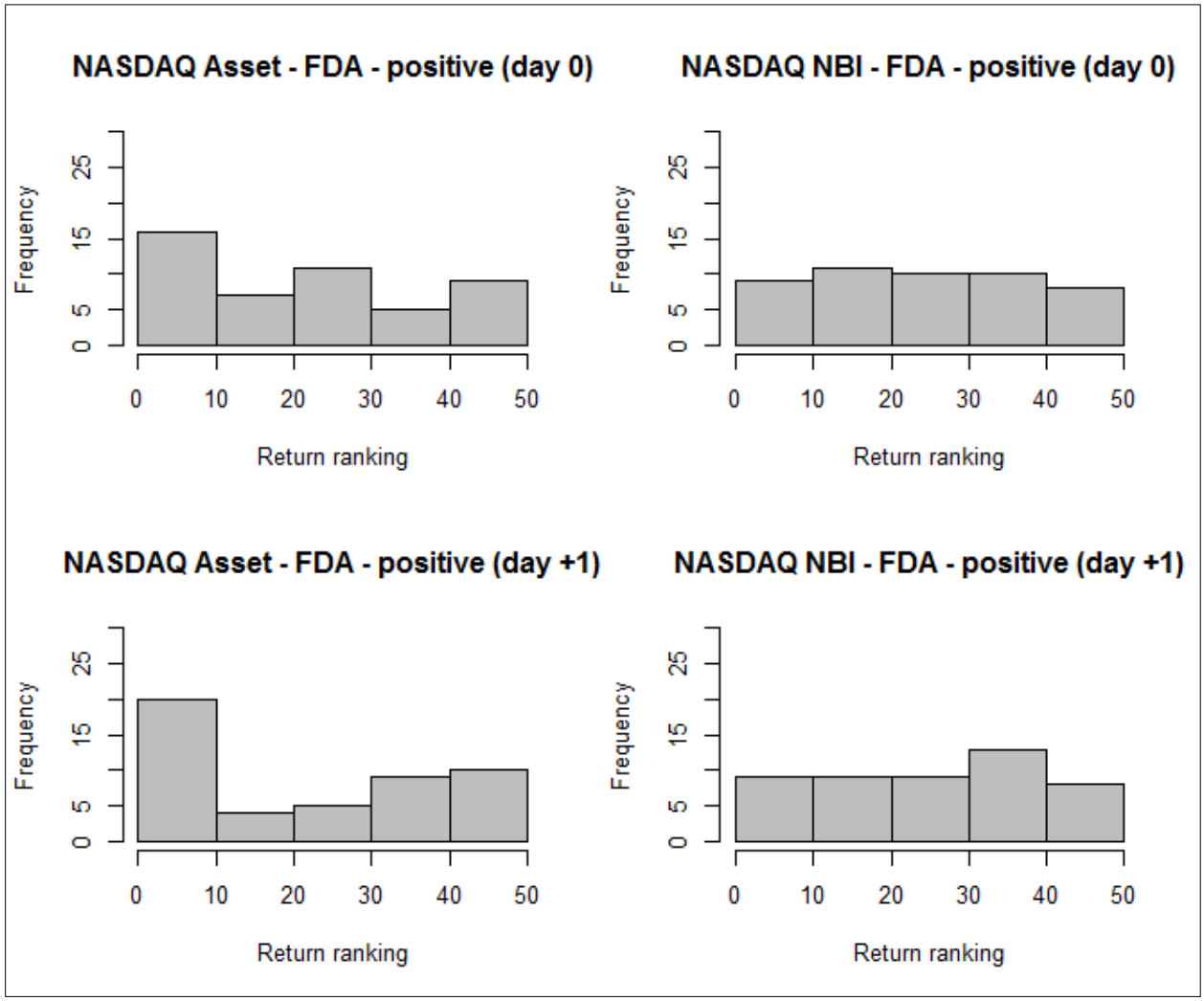
Ticker	Company name
ABT	Abbott Laboratories
AGN	Allergan Inc.
AZN	AstraZeneca PLC
BMY	Bristol-Myers Squibb Company
FRX	Forest Laboratories Inc.
GSK	GlaxoSmithKline plc
JNJ	Johnson & Johnson
LLY	Eli Lilly and Company
MRK	Merck & Co. Inc.
NVO	Novo Nordisk A/S
NVS	Novartis AG
PFE	Pfizer Inc.
SHPG	Shire plc
SNY	Sanofi
TEVA	Teva Pharmaceutical Industries Limited
VRX.TO	Valeant Pharmaceuticals International, Inc.

[Source: http://finance.yahoo.com/q/cp?s=%5EDRG]

Appendix 9: Return ranking distributions of the event window split per day

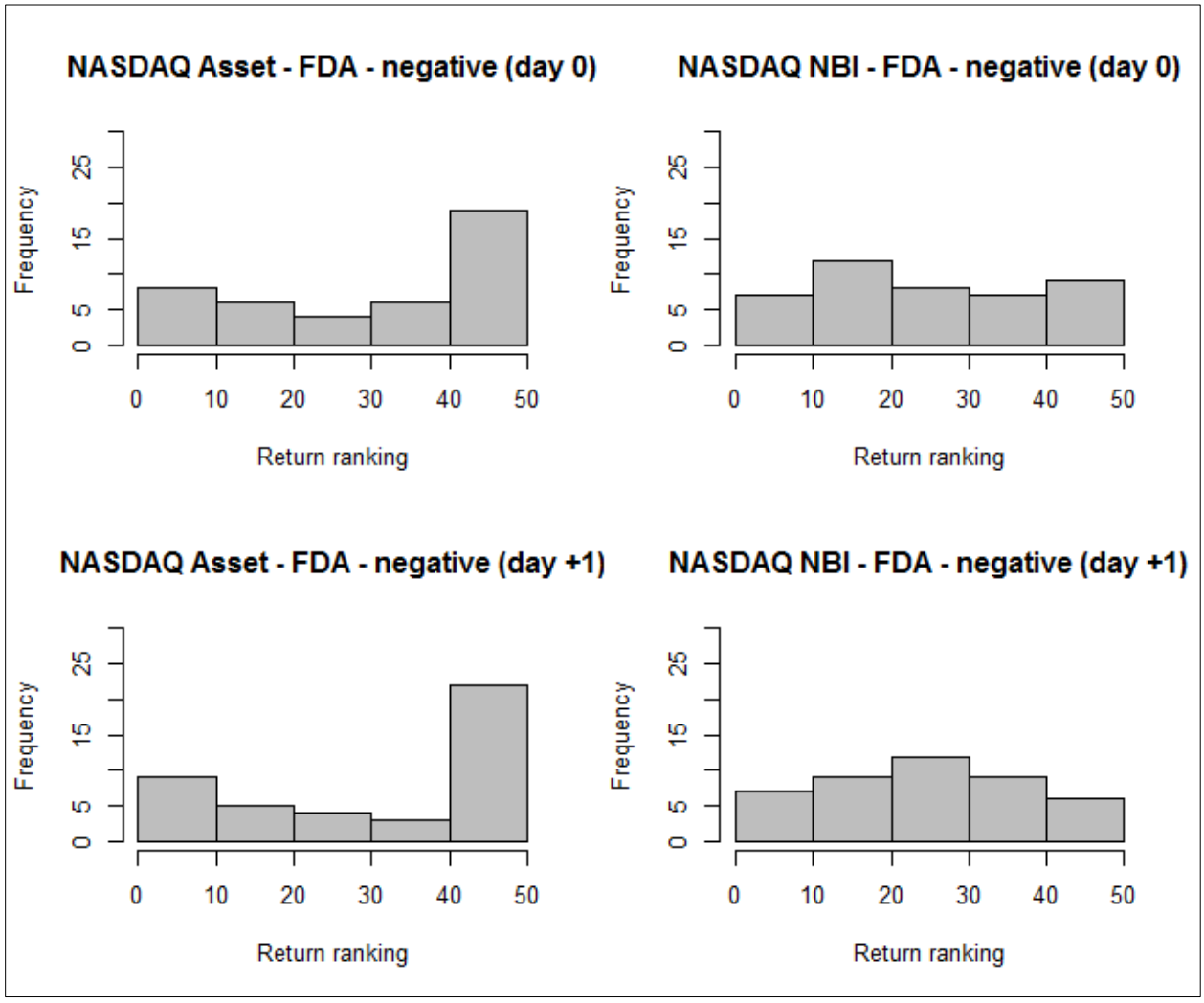
NASDAQ - FDA positive

The distribution of return ranks at day 0 and +1 separately of FDA positive NASDAQ Assets do not significantly differ from the ^NBI return ranks (day 0: p = 0.416; day +1: p =0.1007). Note that in this approach the bias disappears. Also note the 'fat tails' of the index rankings disappear and the distribution is almost completely flat.



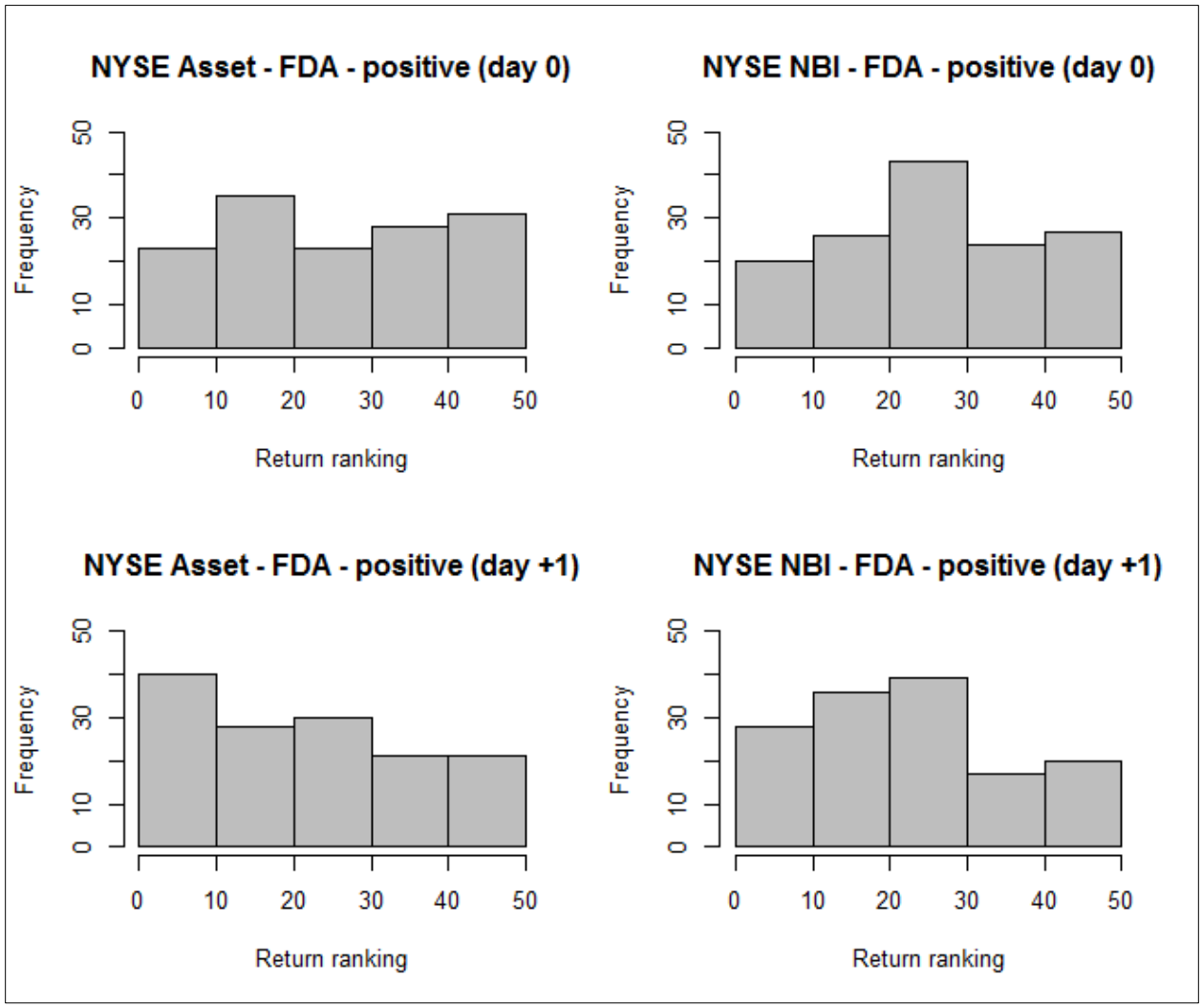
NASDAQ - FDA negative

The distribution of return ranks at day 0 and +1 separately of FDA negative NASDAQ Assets do significantly differ from the ^NBI return ranks (day 0: p = 0.0402; day +1: p =0.0231). An explanation can be that negative news comes more as a shock as the prices clearly anticipate a positive outcome, resulting in a faster and severer downward pressure on stock prices.

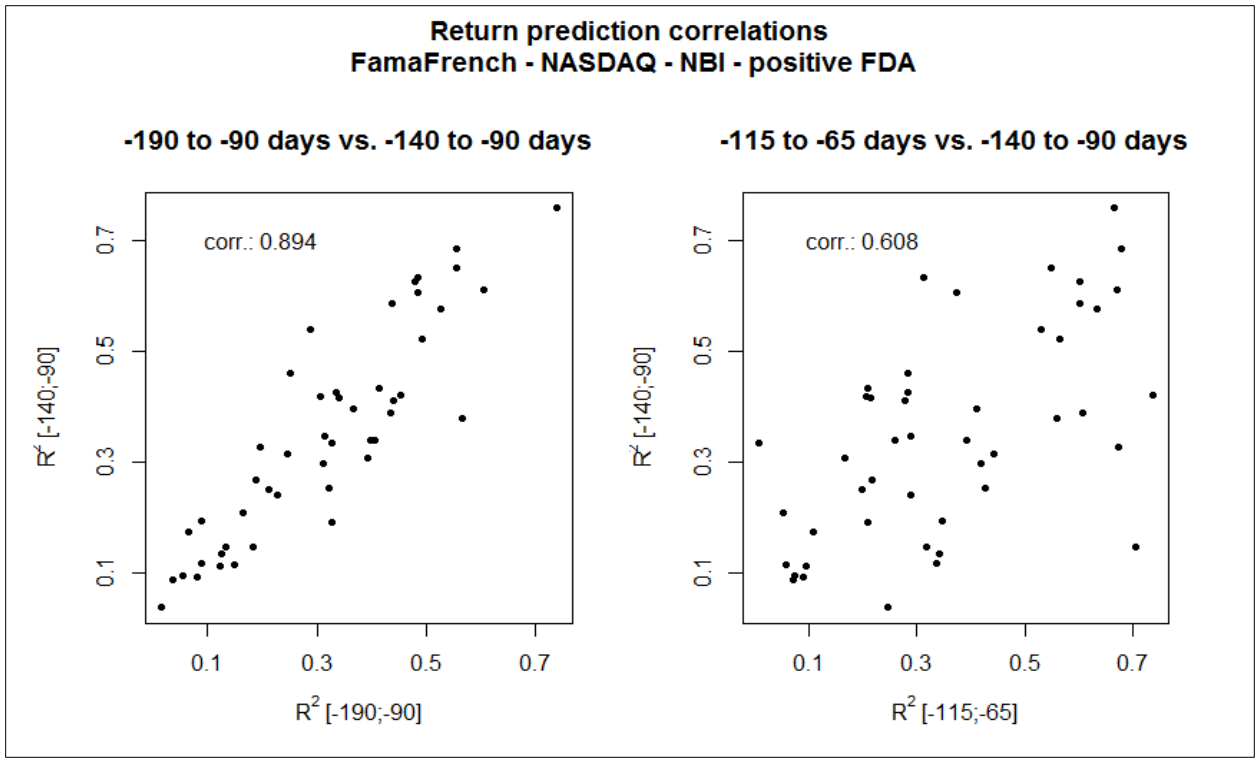


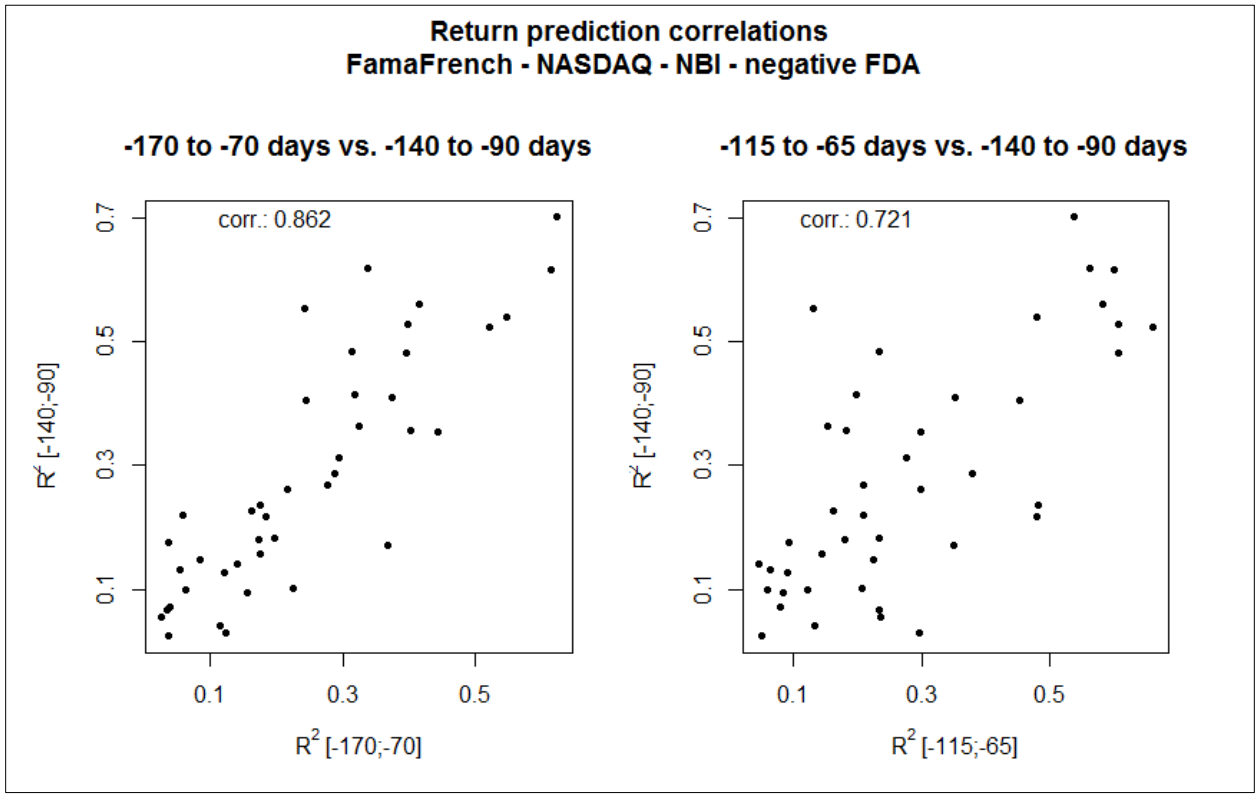
NYSE – FDA positive

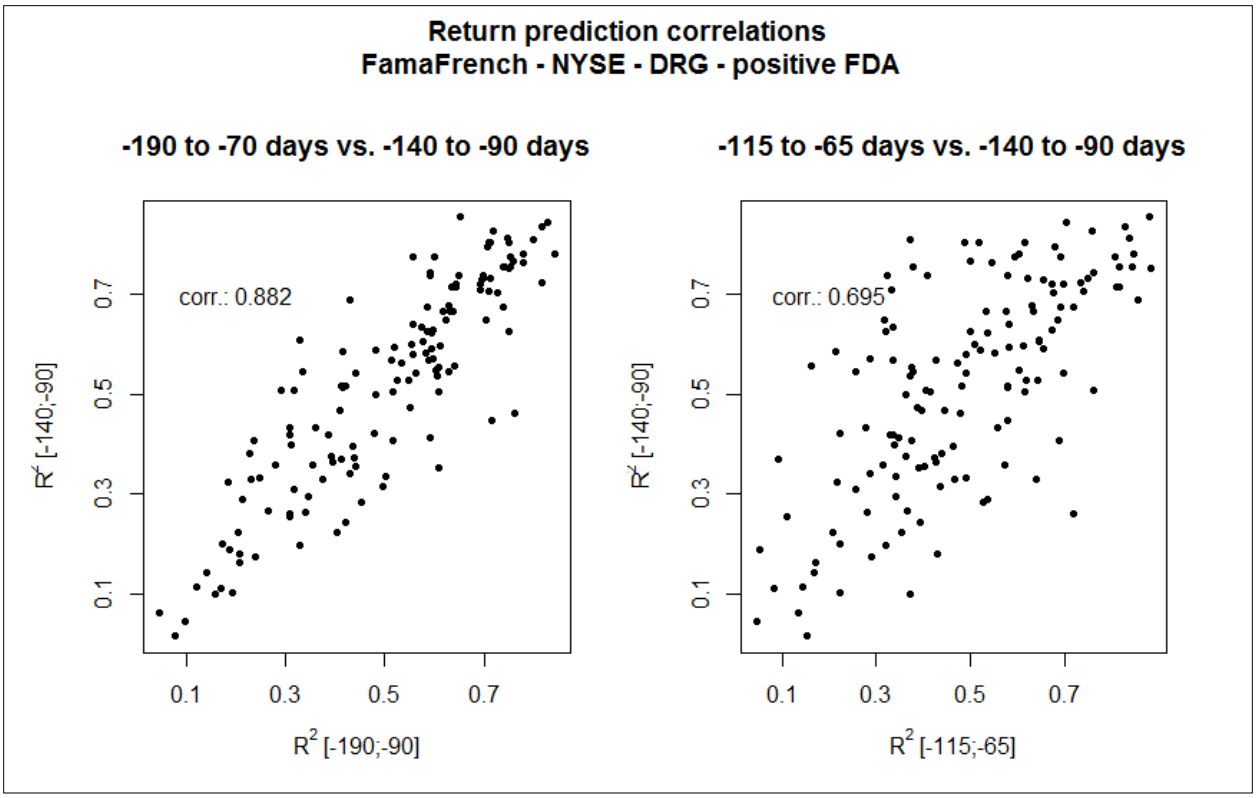
The distribution of return ranks at day 0 and +1 separately of FDA positive NYSE Assets do not significantly differ from the ^NBI return ranks (day 0: p = 0.7453; day +1: p = 0.5658).



Appendix 10: Return prediction correlations of Fama-French R^2s obtained using different training windows.






Return prediction correlations
FamaFrench - NYSE - DRG - positive FDA
-190 to -70 days vs. -140 to -90 days
corr.: 0.882
R² [-140;-90]
R² [-190;-90]
0.1
0.3
0.5
0.7
-115 to -65 days vs. -140 to -90 days
corr.: 0.695
R² [-140;-90]
R² [-115;-65]

Appendix 11: Event study training regression parameters

Fama-French model parameters were estimated in the training window [-140;-90] using the following equation:

$$NR_{it} = \widehat{\alpha_i} + \widehat{\beta_i} * R_{NBI} + \widehat{b_{si}} * SMB_t + \widehat{b_{vi}} * HML_t$$

Estimation parameters are available online: http://www.joachimdeschrijver.be/thesisEW/estimations/.

Appendix 12: Additional CAR calculations in the anticipation window for FDA NASDAQ Assets.

Additional cumulative returns calculated starting at a variable starting point and ending 1 day prior to the announcement date. Both FDA positive and FDA negative NASDAQ Assets were used in the calculations.

CAR type	CAR	t	p-value
CAR(-60,-1)	1,6608	0,2641	0,79233928
CAR(-10,-1)	-2.4785	-1.6253	0.10756524
CAR(-9,-1)	-2.6860	-1.9570	0.05340777
CAR(-8,-1)	-2.4295	-1.9914	0.04943864
CAR(-7,-1)	-2.4144	-2.2618	0.02609225
CAR(-6,-1)	-2.0872	-2.2811	0.02487853
CAR(-5,-1)	-2.3277	-3.0528	0.00297245
CAR(-4,-1)	-2.0349	-3.3359	0.00123215
CAR(-3,-1)	-1.7104	-3.7385	0.00032311
CAR(-2,-1)	-2.0978	-6.8782	0.00000000
CAR(-1,-1)	-1.1630	-7.6264	0.00000000

P-values are calculated using two-tailed student t-distribution.