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NEW PRODUCT DEVELOPMENT IN PERSONALISED MEDICINES:

The Impact of Regulatory Regimes

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Personalised Medicine has become one of the best drivers of research and new product development in the pharmaceutical industry. It aims to develop more safe and efficient therapies with the application of pharmacogenomics. The overall purpose of this study was to compare the regulatory environments of the USA and EU and how they influence new product development in personalised medicine. The objective of the study was to analyse the regulatory requirements at different stages of the drug development process. The study was positioned as exploratory research and data was gathered using desk research approach.

Three streams of literature were reviewed to gain theoretical insight in the topic: Innovation and New Product Development, and New Drug Development. It was found that there are vast differences in the processes and regulations the regulatory bodies of the USA and EU have set for pharmaceuticals and medical devices which do influence the speed in which new drugs and diagnostics devices are commercialised. The study revealed that the US market is more advantageous for commercialising new personalised medicines in comparison to the European market in terms of the speed of the commercialisation process. Another key finding was that the regulatory regimes in the two markets make Europe a more favourable market area for diagnostics companies operating in the field of personalised medicine in terms of speed of the commercialisation process and importance mandated by the regulatory body of combining therapeutics and diagnostics.

KEYWORDS:

Personalised Medicine, Innovation, New Product Development, Drug Development Process

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ABBREVIATIONS

ADR	Adverse Drug Reaction
BLA	Biologic Licence Application
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center of Devices and Radiological Heath
CE	Conformité Européenne (European Conformity)
CFSAN	Center of Food Safety and Applied Nutrition
CHMP	Committee for Medicinal Products for Human Use
CLIA	Clinical Laboratory Improvement Amendments
CMS	Concerned Member State
COMP	Committee on Orphan Medicinal Products
CPI	Critical Path Initiative
CVM	Center of Veterinary Medicine
DHHS	Department of Health and Human Services
EGFR	Epidermal Growth Factor Receptor
EMEA	European Medicine Evaluation Agency
EPAR	European Public Assessment Report
EU	European Union
FDA	Food and Drug Administration
GIST	Gastrointestinal Stromal Tumor
HER	Human Epidermal growth factor Receptor
HIV	Human Immunodeficiency Virus
IND	Investigational New Drug
IVD	In-Vitro Diagnostic
J-I-T	Just-in-time
LDT	Laboratory Developed Test
MRP	Mutual Recognition Process
NCE	New Chemical Entity
NDA	New Drug Application
NME	New Molecular Entity

NPD	New Product Development
OECD	Organisation for Economic Cooperation and Development
PGx	Pharmacogenomics
PgWP	Pharmacogenomics Working Party
Ph+ CML	Philadelphia Chromosome Positive Myeloid Leukemia
PM	Personalised Medicine
PMA	Premarket Approval
PMD	Personalised Medicine Drug
R&D	Research and Development
RMS	Reference Member State
SMD	Small Molecule Drug
USA	United States of America
510(k)	Premarket Notification for Medical Devices

1. INTRODUCTION

1.1. Background

Interest in biotechnology in the development of drugs or even as a substitute method to chemical components has gained significance in the last two decades or so (Simon & Kotler, 2003, 6; PM Coalition Report, 2009).

Generally, the biotechnology industry is a growing industry. For instance despite of the financial crisis that hit the global economy in 2008/2009, the biotech industries have been experiencing growth. According Ernst and Young's Global Biotechnology report (2009, 16), the developments in the industry have been influenced, in large part, by" four sweeping paradigm-shifting trends of generic drugs, expansion of personalised medicine, health care reforms in the USA and the continued globalisation of the industry".

Interest in personalised medicine took off after the human genome project and since then, both the pharmaceutical and biotechnology industries have shown significant interest and progress in its development and application. It is arguably one of the best drivers of research and new product development in the pharmaceutical industry. The concept refers to the use of an individual's molecular information when trying to match right patients with right drugs in terms of efficacy and safety.

Being an evolving area of science and practice, personalised medicine drugs (PMDs) have faced both acceptance and criticism. On one side of the aisle, supporters of PMDs see a future where they will make health delivery more medically and cost efficient (Ginsburg & McCarthy, 2001; PMC report, 2009). On the other side, critics see PMDs as crossing the ethical boundaries of science and medicine (Dion-Labrie et. al, 2010).

Literature abound on drug development process is based mainly on traditional chemical-based drug development, and even in biotechnology generally (Gupta et al, 2007;

Styhre, 2006; Thomas, 1994). However, due to the special nature of PMDs and its rising significance in the pharmaceutical industry, a new academic interest is evolving that focuses on product development in the field of PMDs (Bock et al, 2000; Ginsburg & McCarthy, 2001; Hopkins et al, 2007). Would the process be influenced by the same scientific, policy and market forces that shape drug development in other areas of the pharmaceutical industry?

In the light of the above question, and given my personal interest and internship in a Biotech Service company with focus on the PMD industry, this study seeks to explore the trends in the development of selected drugs in the PM field and their launch in both the US and European markets. Though there is growing evidence of advancements in emerging markets such as India and Brazil, evidence shows that the majority of the biotechnology companies, in terms of size, market capitalisation and activity, are still located in Europe and USA.

The study will employ conceptual wisdom from theories of Innovation and New Product Development and International Business to analyse the global trends in the industry specifically with regards to the regulatory environments for PMD New Product Development.

It is expected that the results would contribute to our understanding of the external regulatory environment influencing industry developments generally and PMDs specifically.

1.2. Research Questions

The overall purpose of the study is to compare the regulatory environments of the USA and EU and how they influence new product development in personalised medicine. Specifically the following objective has been set for the study:

To analyse the regulatory requirements at different stages of the drug development process.

The above objective would be met with the following questions:

1. What is the duration of the review process for granting Marketing Approvals in the US and in the EU?
2. What is the time lapse between Marketing Approval and Launch of a new pharmaceutical in the US and in the EU?
3. What is the time lapse between the Launch of a new drug and the Launch of a biomarker test developed to assist with medical decisions related to the drug in the two markets?

The research questions assume differences in the regulatory regimes of the USA and EU and that these differences might be significant in the new drug development process.

2. LITERATURE REVIEW

The study takes theoretical wisdom from three streams of literature: Innovation and New Product Development, and New Drug Development. This chapter reviews existing literature in the three areas and draws implications for personalised medicine.

2.1. Innovation and New Product Development

Innovation has been researched by many academics through the years, hence there are numerous descriptions varying from exceedingly wide definitions to narrower ones depending on the interests of the authors. The meaning of the term innovation has evolved in the past 40 years from being considered merely as an idea or a process causing change to the widely accepted definition of a new concept needing to be successfully developed and commercialised in order to become an innovation.

In its widest sense, innovation can be anything that is new to a business (Abernathy & Utterback, 1978). However, no matter how innovation has been described, the perception of newness to the parties involved in the process has always been part of it (Cumming, 1998). For instance, Van de Ven (1986, 591) adopted this approach stating that " An Innovation is a new idea, which may be a recombination of old ideas, a scheme that challenges the present order, a formula, or a unique approach which is perceived as new by the individuals involved".

2.1.1. Types of Innovation

In 1943, Schumpeter used the concept of radical innovation triggering the process of transformation in his economic theory which describes the impact innovations have on industries and economies. He divides innovation into groups depending on the type of innovation in question: introduction of a new commodity or production method,

opening a new market, changing the source of supply and reorganisation of an industry (Schumpeter, 1964, 59). The first two, introduction of a new product/production method and opening a new market, are considered technological innovations due to their economic output.

To elaborate Schumpeter's categorisation of different types of innovation, Cumming (1998) and Hine & Kapeleris (2006, 5) identify four types of innovation: product innovation, process innovation, market innovation and technology innovation. To distinguish the different types of innovation even further, Trott (2005, 17) has written about organisational innovation, management innovation, production innovation and service innovation.

According to Hine & Kapeleris (2006, 5), product innovation can be either major or incremental in nature. A product considered as a major product innovation is a commercialised invention which has been developed from entirely new ideas. However, this description has its limitations. For instance, even though one would be the first to create a new technology product, it is possible that the idea of the same or very similar invention has been in the minds of many, yet has not reached the development stage due to lack of technical aspects required (Cumming, 1998). Incremental product innovation differs from major product innovation in the idea generation phase. An incremental product innovation does not need to be developed from a radical idea but from a creative input added to enhance an existing product. As an example, developing a product with substantial improvements compared to an existing product either technically or economically.

High level of competition in all markets forces companies to constantly think of ways to improve their performance. Already in 1974, Robertson wrote about innovation, describing it as "a series of technical, industrial and commercial steps"; process innovation. Process innovation's purpose is to create new methods for the production stage of new product development, aimed at enhancing the quality of the product and/or enable the product to be made with a lower cost and/or in a less time consuming manner. However, the process ought to be executed in such a way that improving one

variable would not result in drawbacks on others. For instance, cutting costs should not consequent in jeopardising the quality of the product (Cumming, 1998).

Trott's analysis (2005, 17) distinguishes process and production innovation with the notion of process innovation being related to manufacturing processes, in comparison to production innovation; meaning new systems related to manufacturing, such as the just-in-time (JIT) system.

Another type of innovation, besides product; process; and production innovation, is market innovation. Companies use market innovation with the aim of finding new potential markets, and new ways of serving their target markets more efficiently. The process of market innovation begins from identifying potential markets which can be done through careful market segmentation. The segmentation can be conducted by choosing an objective variable such as a particular geographic area or a subjective variable such as data describing consumer and buying behavior (Johne, 1999). For example, consumers make buying decisions based on social, cultural, personal and psychological factors depending on the type of product needed. The four different types of buying behaviour: complex buying behaviour, dissonance-reducing buying behaviour, habitual buying behaviour and variety-seeking buying behaviour, can be used to segment consumers in groups in order to turn potential customers into actual market opportunities (Kotler et al, 2005, 276-278).

Organisational- and management innovation deal with in-house procedures in businesses. Organisational innovation includes various systems and procedures taken upon in organisations in order to improve its activities, whereas management innovation consists of managerial systems such as total quality management (Trott, 2005, 17). Service innovation Trott describes as the new field in innovation enabled by the internet, for example financial services that are internet based belong to this category.

A slightly differing approach for categorising innovation types was proposed by Damanpour in the early 1990s. He classifies innovation as either technological or non-technological, also in consistence with the Schumpeterian approach, but the main

determinant of further sub-grouping is whether the innovation is considered technological or not. This is opposed to all different types of innovation mentioned above not segmented according to the features of the innovation but a more general typing. Therefore, technological innovation is further segmented to subgroups including products, services and processes, whereas non-technological innovation includes organisational processes and administration systems (Damanpour, 1991, 556).

In literature on technological innovation, the term itself has also been used by many authors to describe the process a new technological product goes through starting from the idea generation, moving through the development of the product with the help of sciences into a finalised item; new product development (Styhre 2006; Cantisani, 2005). Besides, Styhre (2006) suggests that there is a relationship between scientific thinking and managerial objectives in science-based innovation in the pharmaceutical industry and that "innovation is very much the identification of the best possible fit between the favored problem definition and its suggested solution". His view echoes to a large extent the study published by the Organisation for Economic Cooperation and Development (OECD) on innovation, which describes innovation as a process starting from identifying a new market opportunity for a technology-based invention which will be developed, produced and marketed with the aim of commercial success (OECD, 1991).

2.1.2. Innovation Models and Adoption

In literature examining innovation, several models describing how innovation takes place have been introduced. The technology push model is a linear model which describes new product development as a sequential pattern beginning from inventing a new product, manufacturing followed by marketing activities, and consequently the product finding its way to the users. The technology push model was very popular after the Second World War, but in the late 1970s the importance of the needs of the market were emphasised and the market pull model was created. The market pull model is also linear yet the sequences happen in different order, starting from marketing (the needs of

the market investigated through communication with users of a particular product), after which the R&D activities and manufacturing take place, resulting the product ending up to the users. In addition to the technology push and market pull models, the simultaneous coupling model identifies manufacturing, marketing and R&D as the three functions that support the birth of innovation simultaneously, but on the contrary to the linear models, does not state the exact starting point (Trott, 2005,22-24, Schumpeter, 1964, 58-62).

The interactive model of innovation combines both of the linear models; technology push and market pull, but states that albeit the process would be sequential, it may not be continuous. The interaction comes from a flow of feedback originating from communication paths that provide information on the needs of society and marketplace, and also information on the latest scientific and technological advances in society (Trott, 2005, 24-25).

The technology push model is descriptive of the traditional drug development process, considering the sequential path of phases starting from R&D, moving on to manufacturing and commercialisation of the new product. In addition, traditional drug development process aims to develop products for a large population to treat a certain disease or medical condition. It can be speculated that the new product development for personalised medicine drugs (PMDs) leans more towards the market pull model, seeing that the PMDs can be developed according to genotype and/or other individual characteristics to fit the needs of individual patients (Jain, 2009, 1).

The diffusion of innovation theory by Rogers (1962, 2003) seeks to explain how innovations are adopted by individuals. He defines diffusion as "the process by which an innovation is communicated through certain channels over time among the members of a social system" (Rogers, 1963, 2003; 5). In his theory the importance of understanding the needs of different types of consumers transfers into subgroups of "adopters": innovators, early adopters, early majority, late majority and laggards, with varying timescale of diffusion respectively. The concept of re-invention is also central to the theory, describing how the occurring change does not necessarily happen in the

individuals using a particular innovation but in the innovation itself. This can be seen as an ongoing process of users improving the product to suit their needs best (Rogers, 1963, 2003; 180, 281).

In my study I adopted the definitions of OECD (1991), Rogers (1962, 2003), and Styhre (2006) that innovation is a process of successfully developing and commercialising a technology-based invention, adopted by different types of users in a varying order. In the pharmaceutical industry, new product development is fundamentally finding biomedical solutions to biomedical problems (Styhre, 2006).

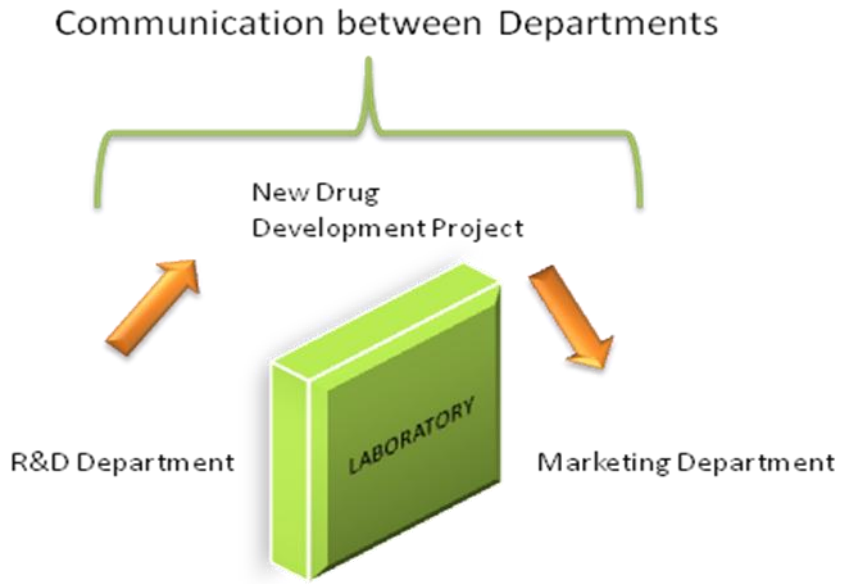
2.2. New Product Development Models

The concept of new product development describes the stages it takes for an idea to be turned into a tangible product and commercialised in a chosen market. The stages involve generating a new idea, developing a concept based on the idea, manufacturing the product and creating a business strategy around it (Yelkur & Herbig, 1996). In order to explain the phenomenon of new product development using different methods, several models have been created. These models illustrate how there can be various routes on the way to the final destination of introducing a new product to the market. According to Saren (1984), there are seven distinct categories that comprise various models of new product development: departmental-stage models; activity-stage models and concurrent engineering; cross-functional models; decision-stage models; response models; network models; and conversion-process models.

The Departmental Stage Model describes the path of developing a new product as various separate processes taking place in a highly compartmentalised environment. The first stage of the process would be the responsibility of a company's R&D department, the second stage, development of the product, the responsibility of the manufacturing department and commercialising the product would be handled by the marketing department. Yet, Trott (2005, 400-401) thinks separating the stages of the development

process into responsibilities of different departments, according to the activities required to complete a stage, within a company can have negative outcomes. For instance, if the communication channels between each of the departments do not work, the whole development process can slow down or the quality of the product may be compromised. Figure 1 describes how a Departmental Stage Model would look like if used in drug development environment.

Figure 1 Departmental Stage Model



Source: Based on Trott, 2005, 400

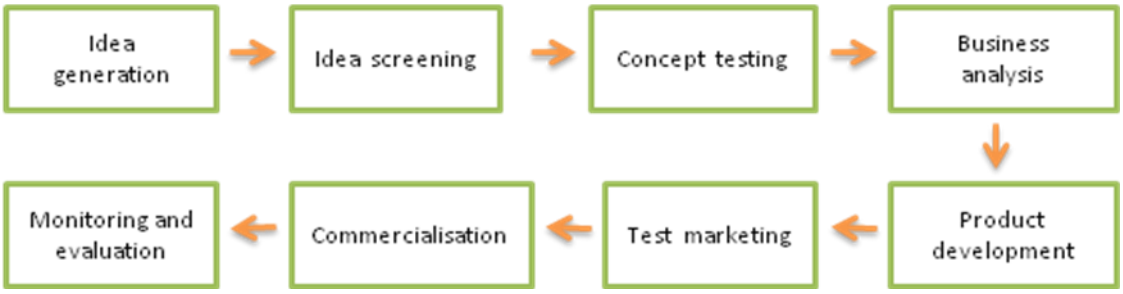
The Departmental Stage Model would describe new product development in the pharmaceutical industry happening within three different stages. The R&D department would be responsible for discovering a new drug, after which the drug would be developed in a laboratory environment, after which the marketing department would take care of commercialising the product.

It can be noted that such a linear model may not necessarily result in commercial success, unless there is high level of communication between the departments; marketing department informing the R&D department of the current needs of the market and vice versa. However, this model does not guarantee high level of communication but relies on the expertise of each individual department.

Activity Stage Model is another model used to describe the stages occurring in new product development process. The model sees new product development as separate activities taking place along the way of developing a product. The first stage of the process is idea generation, followed by idea screening. Idea screening is used in order to separate viable ideas that could be developed and hopefully generate revenue for a company, from ideas that may not work in real life. Only a fraction of the total number of ideas created, survive the screening process, which are then developed into concepts and further tested.

Once the ideas that qualify after the screening process have been chosen, business analysis can be conducted. This is done before the initial product development begins in order to minimise risks in terms of the likeliness of the product to succeed in the market. Once the product has been developed, it will be test marketed which means a chosen consumer group, sample, will use the product. Based on the results of test marketing, the company developing the product still has a chance to change some of the features in the product in attempt to please the consumers more, based on the recommendations given by the sample group. The final stages of the Activity Stage Model are commercialising the product and monitoring and evaluating its success. By commercialisation, making the product available in the mass market is meant. Figure 2 demonstrates the activities occurring in the Activity Stage Model.

Figure 2 Activity Stage Model



Source: Based on Trott 2005, 398

The Activity Stage Model suggests that new product development happens in stages that follow each other in a consecutive order. The Activity Stage Model describes rather well the traditional process of new drug development, focusing on activities taking place in a sequential order. The concept of Activity Stage Model stresses the importance of communication between activities, in comparison to the less communication focused Departmental Stage Model. According to Trott (2005, 400-402), continuous communication across activities taking place in the Activity Stage Model improves the efficacy of the process.

However, activity-stage models by other authors (e.g. Crawford, 1997) have realised that some of the stages might happen in parallel with varying levels of intensity in the stages. Hence, it can be speculated that such models are leaning towards the cross-functional models. Cross-functional new product development models utilise the know-how of people working in different departments of an organisation. According to the concept of Cross-Functional models, a high level of communication between different actors in the process enables the parallel occurrence or integration of the stages in the process of new product development (Trott, 2005, 402). The Concurrent Engineering models were also created to explain the simultaneous occurrence of different phases yet they do not place the importance of communication as high as does the Cross-Functional models.

Another way of explaining new product development is the Decision Stage models. According to Cooper & Kleinschmidt (1993), Decision Stage models explain new product development as a series of decisions taken along the process. These models bear similarity to the Activity Stage models in the sense that communication is an ongoing process including a high level of communication between the stages. Perhaps the most market-oriented models would be Response Models which concentrate on getting feedback from organisations or individuals about the new ideas before the initial new product development begins (Trott, 2005, 403).

Already in 1967, Schon introduced the idea of Conversion-Process Model in new product development. He describes new product development as a conversion of inputs

from different sources into a substantial output; the product. Network Models illustrate a fairly similar view to this on how new products are being developed. Network Models accept the idea of various sources being needed in order to be able to develop a new product. However, Network Models are slightly more specific on the sources businesses could use, than the Conversion-Process Models, stressing the impact of using not only internal, but also external sources in NPD. Trott (2005, 403) echoes the views of Conversion-Process Models and Network Models stating that NPD should be perceived as "a knowledge accumulation process requiring inputs from a wide variety of sources".

The NPD Models described in this chapter explained the different schools of thought on how new products are being developed. The Departmental Stage Models and Concurrent Engineering Models emphasised the expertise of the employees working in their specific fields, whereas Activity Stage, Cross-Functional, Decision Stage and Network Models placed the emphasis on high level of communication. The Conversion-Process and Network Models highlighted the fact that sometimes also sources from outside of the company developing the new product might be needed, whereas the other models were more concentrated on the processes taking place within an organisation developing a new product.

The development of new drugs requires the ability to use and explore life sciences combining theoretical models and frameworks with material resources and entities in a laboratory environment (Styhre, 2006). Still, in order to understand the complexities of new drug development, models such as Activity Stage Models and Cross-Functional Models, can break the process in stages making it easier to comprehend.

New drug development incorporates the use of technology and science. Trott (2005, 18) defines science as "systematic and formulated knowledge" and advocates that "technology comes from employing and manipulating science into concepts, processes and devices". Lynch (1988) elaborates stating that scientific work is not only discovering new objects, but requires "making such entities appear as immutable and ontologically stable, entities that can be tested and modified in laboratory practice."

This concept depicts well the new product development process in the pharmaceutical industry described more in-depth in the following chapter.

2.3. Understanding the Drug Development Process

The process of drug development is more complex than traditional new product development process due to the integration of science and technology in the stages. Yelkur & Herbig (1996) define the steps of traditional new product development as idea generation, screening, concept development and testing, marketing strategy, business analysis, product development, market testing and commercialisation, in line with the activity stage model presented in the previous chapter. They also distinguish traditional new product development from the development process products aiming for global markets require, with the notion of the stages being integrated in the latter, opposed to the stage-by-stage approach.

This distinction bears similarity to the new product development (NPD) process for pharmaceutical products by the means that although the NPD process is often described linear, the stages can sometimes overlap or happen in parallel. For instance, preclinical testing and development can sometimes be continued even though the clinical trials would have begun (Hine & Kapeleris, 2006, 191). Having the scientific knowledge to pursue the structured process of new drug development and understanding the regulatory environment which controls the process most of the way, are key factors in successful new product development in the pharmaceutical industry.

Doranbje et al. (1998) lay the basis of new drug development on structured management procedures and factors such as novel forms of thinking, designing creative solutions to practical problems and coming up with new applications of knowledge that have been taken for granted previously. This view was also adopted by Sundgren & Styhre (2004) who state that the development of new drugs relies heavily on formal knowledge and

expertise in relevant scientific domains, for example medicine, pharmacology and biology.

Personalised medicine is a fairly new approach to healthcare. Its main purpose is to match right patients with the right drugs using person's genomic information, in order to reach the highest levels of efficacy and safety possible. For personalised medicine drugs the new drug discovery and development processes are often accompanied with pharmacogenomics (PGx); applying genomic technologies in the drug discovery process or characterising existing drugs further (Barnes, 2007, vii). Integrating diagnostics, such as biomarker assays to a particular medicinal therapy can help to identify patients most likely to benefit from the treatment. Hence the term personalised medicine drugs covers both types; genomic-based drugs and combinations of therapeutics and diagnostics (Jain, 2009, 1).

In literature on new drug development, small differences in the models of the process can be detected, yet the basic elements of the stages remain the same due to the basic technology behind the process and the highly regulated nature of the industry. Ginsburg & McCarthy (2001), distinguish the traditional linear model to drug development from the integrated model personalised medicine often uses. The traditional model begins from target discovery and validation, moving on to lead discovery and optimisation, followed by pre-clinical and clinical trials after which the drug sponsor would apply for marketing authorisation and introduce the new drug to the market. The traditional model can be seen fairly linear, even though some of the stages may happen in parallel.

The integrated model differs from the traditional model in two ways. The stages in the model can either be exactly as in the traditional model, or the process can begin from pinpointing a gene that influences specific proteins in cells that are responsible for a disease developing, whereas in the traditional drug development model the process begins with identifying the disease causing proteins (target discovery). The other difference in the traditional and the integrated model is in the sequence the stages take place in. The integrated model is not linear but more of an ongoing cycle where the drug can be further improved even after it has been launched to the market by either by

redesigning the actual drug formula or by developing a diagnostic test to increase the medical benefits of the drug (FDA, 2010 [referred 7.7.2010]; Ginsburg & McCarthy, 2001; Gupta et al., 2006; Hine & Kapeleris, 2006, 191-193; Styhre, 2006; Walsh, 1998, 38).

The NPD process of pharmaceuticals can be divided in three stages: research/discovery stage, development stage and commercialisation stage. Biotechnology is used in developing genomic-based drugs and biomarker diagnostic devices, which is why the emphasis in the NPD process of pharmaceuticals described in this thesis is on NPD of biopharmaceuticals. The following two chapters will describe the stages and the activities taking place during the stages in more detail.

2.3.1. From Science to Product

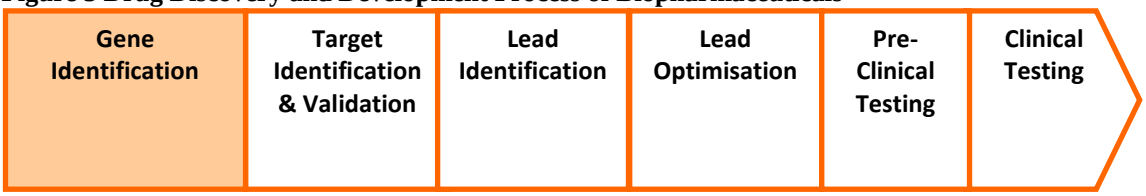
The process of drug development consists of the integration of scientific and technological knowledge. The whole process of drug development begins with discovering a new objective which will be developed into a new pharmaceutical.

Drugs can be divided in two separate groups based on where they have been derived from: small-molecule drugs (SMDs) which includes new chemical entities (NCEs), also known as new molecular entities (NMEs); and biological drugs (Turner, 2007, 3). The term “biopharmaceuticals” can refer to biological drugs; drugs derived from biological sources (living organisms) or molecular entities that have been produced using biotechnology. Biological drugs are either protein- or nucleic acid- based (Walsh, 1998, 2-3). To distinguish between the two in this study, in order to avoid confusion, the term biopharmaceuticals will be used to refer to NMEs produced using biotechnology and the term biological drugs to refer to drugs that have been derived from biological sources. Personalised medicine drugs can be both SMDs and biological drugs.

The research/discovery stage constitutes of the activities of gene identification, target identification and validation, and lead identification. The Development Stage occurs after the discovery stage and includes the activities of lead optimisation, biological

testing and clinical testing (Figure 3). The Commercialisation Stage is the last stage in the NPD process and it includes applying for marketing approval from a regulatory authority and launching the product. The new product development process for pharmaceuticals is traditionally considered linear but stages can also occur in parallel.

Figure 3 Drug Discovery and Development Process of Biopharmaceuticals



Source: Based on Markiyannis & Biegel, 2004, 4

The research/discovery stage for biopharmaceuticals includes various activities: gene identification, target identification and validation, and lead identification. Drug discovery of biopharmaceuticals uses typically a certain disease as a starting point, whereas traditional drug discovery would use treatment, hence skipping the disease gene identification stage, otherwise following the same model (Dennis & Gallagher, 2001, 135; Hine & Kapelaris, 2006, 191).

The first activity of the drug discovery stage is identifying a disease gene. The disease gene is a gene that affects specific proteins in cells which are responsible for the development of a disease. Dennis & Gallagher (2001, 135), define genes as an "ordered sequence of nucleotides located in a particular position on a particular chromosome that encodes a specific functional product". Using the method of positional cloning, it is possible to identify disease genes of unknown biochemical function. Thus, a "disease model" is employed to identify relevant genetic or biological targets (Dennis & Gallagher, 2001, 123). In practice, this means finding the protein influenced by the already identified gene.

The sequencing of the human genome has enabled the creation of an extensive pool of potential molecular targets which can be used to assist in the activity of identification. The drug targets are normally proteins (complex molecules, e.g. receptors for hormones

or specific enzymes) that are causing malfunctions in cells that consequently result in disease on individuals (Walsh, 1998, 41; Hine & Kapelaris, 2006, 191-193). When a target has been identified, it will need to be validated which means determining if the target is critically involved in the disease, and thus viable of being further developed.

The next activity in the research/discovery stage is the lead identification which means finding lead(s), for instance molecules or chemical compounds, which interact with the identified target with the aim of inducing a desired therapeutic effect (Styhre, 2006). This interaction means the lead being capable of attaching itself to the target protein and starting to block the receptors or other active sites in the malfunctioning target. The lead molecule can be identified either with using the technique of high-throughput screening of a large library of chemical compounds, or natural products for biological drugs, or using the method of de novo design. De novo design means developing a novel lead molecule analysing the three-dimensional structure of the target molecule (Markiyannis & Biegel, 2004, 4).

The Development Stage of NPD of pharmaceuticals can begin after the activities described in the discovery stage have been completed. The first activity in the Development Stage is optimisation of the identified lead. The lead can be optimised using biological testing and chemical synthesis (Markiyannis & Biegel, 2004, 4). The activity in the NPD of drugs that follows lead optimisation is preclinical development and testing. This includes various pharmacological analyses that examine the new drugs suitability to be moved on to the clinical research stage. Walsh (1998, 53) defines pharmacology as the study of the features of drugs and on the effect they have on humans. Preclinical development and testing are done on an animal model and includes various tests such as toxicity and mutagenicity tests that show whether the drug is safe to be tested on humans (Walsh, 1998, 53-55; Styhre, 2006). Mutagenicity tests are conducted in order to examine if the drug can damage DNA and are used mainly in the development process of chemical based drugs, whereas for biological products such tests can be performed after additional substances have been added to the drug formulation (Walsh, 1998, 55).

For personalised medicine drugs the new drug discovery and development processes are often accompanied with pharmacogenomics (PGx); applying genomic technologies in the drug discovery process or characterising existing drugs further (Barnes, 2007, vii). In the drug discovery phase, PGx can be applied with the attempt of discovering more efficient drugs; drugs designed to target specific genomic subgroups or drugs that target all subgroups.

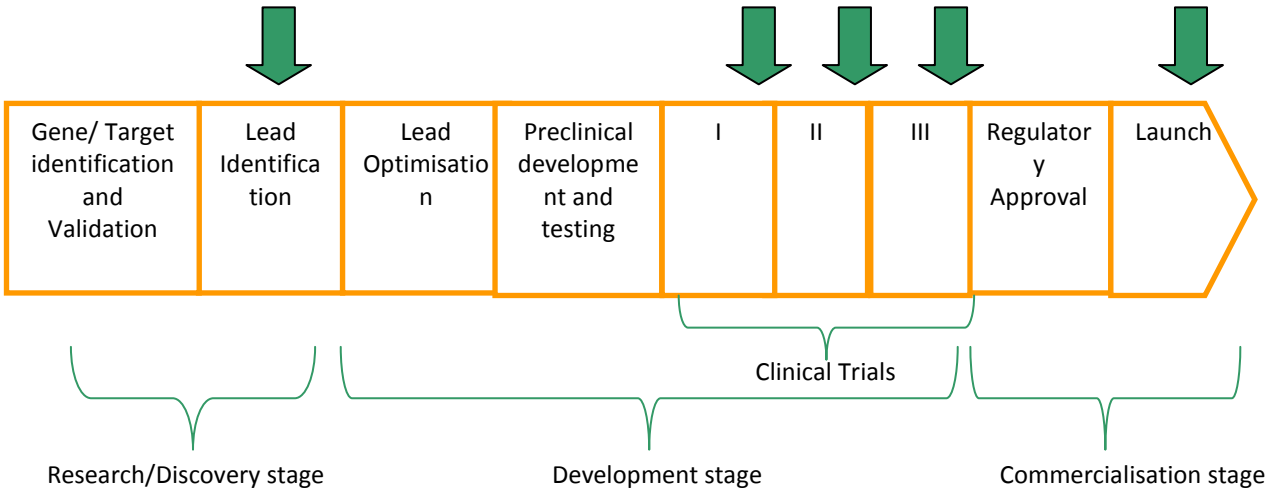
After the preclinical trials, the drug sponsor (research institutions, companies and other organizations responsible for the drug development) presents the findings of the preclinical trials to appropriate regulatory bodies, either the US Food and Drug Administration (FDA) in the US market or the European Medicines Evaluation Agency (EMEA) in the EU. However, often companies cooperate with regulatory agencies even before this point in order to be on the same page with the regulator on the requirements. For instance, in the USA an Investigational New Drug Application (IND) needs to be submitted to the FDA by the sponsor and if reviewed successfully, the clinical trials can start.

The next activities of the Development Stage of the NPD process are the clinical trials. Clinical trials are divided in three phases and always happen in the sequence of Phase I, Phase II and Phase III. In the first phase of clinical trials, 20 to 80 clinical trials subjects are needed to participate in assessing safety of the drug in relation to dosage and side effects. In the first trial it is also common to research how the drug is metabolised and excreted.

If the Phase I results are favorable the sponsor can move on to the next stage. Phase II trial, in which the data is gathered from 100 to 300 clinical trial subjects, establishes preliminary information on the efficacy of the drug and additional information on drug safety. Again, if the second phase is completed successfully, proving that the drug is effective in people who have a certain disease or medical condition, the development process can progress to the third phase of clinical trials.

The third phase requires the most clinical trial subjects with 1000 to 5000 people participating in the trial. The purpose of the Phase III trial is to test and compare the new pharmaceutical product with combinations of drugs or with an existing standard therapy, expand the knowledge already gained on the drug's safety and efficacy and to test the drug with different dosages and populations (Hine & Kapelaris, 2006, 191-193; FDA 2010[referred 7.7.2010]). Figure 4 depicts the stages of traditional drug development and also points out the stages in which PGx can be applied when developing personalised medicine drugs.

Figure 4 Applications of PGx during Drug Development



Source: Based on Kapeleris et al 2004; Webster et al, 2004

Pharmacogenomics can be used in the lead identification phase to find allelic variants of drug target in order to discover drugs for specific genomic sub-groups. In clinical trials PGx can be applied in order to improve the safety and efficacy of new drug in development. Recently, PGx has also been employed to improve safety and efficacy of already licensed drugs. The technology has helped further research on some drugs to segment patients to genomic subgroups to screen out those most likely to experience adverse drug reactions (ADRs). This has enabled drugs that have been restricted from being marketed due to severe ADRs in certain patient groups to access the market with PGx information added in the drug's label (Webster et al, 2004).

2.3.2. Regulations of Commercialising New Pharmaceuticals

After the clinical trials have been conducted, the sponsor needs to apply for marketing approval for the drug. In the USA, the Food and Drug Administration (FDA) is responsible for reviewing Therapeutic Biologic Licence Applications (BLAs) for biological products and New Drug Applications (NDAs) for NMEs, both of which include all animal and human data, the analyses of the data and information on how the drug has been manufactured and its effects in the body. After the FDA has received the appropriate application, they have 60 days to decide if they find the information provided by the sponsor substantial enough to proceed reviewing it. According to the FDA's Center for Drug Evaluation and Research (CDER), 90 percent of standard drug NDAs are reviewed and acted upon in 10 months after the application has been received. (FDA 2010[referred 7.7.2010]).

The FDA was established in 1930 and has been an official government agency as part of the US Department of Health and Human Services (DHHS) since 1988. The regulations given by the FDA are based upon the legislation from the Federal Food, Drug and Cosmetic Act (Walsh, 1998, 62). The agency operates in several fields which is why its functions have been divided in several departments. Besides CDER, the Center for Biologics Evaluation and Research (CBER) handles drug approvals, with in principle CDER evaluating small molecular drugs and CBER mostly biological drugs. However, the CDER sometimes reviews biological products as well. The Center of Devices and Radiological Health (CDRH) is responsible for evaluating medical devices, for instance diagnostic tests, whereas the Center of Veterinary Medicine (CVM) and Center of Food Safety and Applied Nutrition (CFSAN) are specifically focused in animal drugs and food safety issues respectively (Walsh, 1998, 62).

Whether it was the CDER or the CBER appointed to review the marketing application of a new drug, the review process is the same. The review team who conduct the primary review consists of experts of different fields such as chemists, medical doctors, pharmacologist and microbiologists who evaluate the studies conducted that ought to

establish the safety and efficacy of the drug. The review team also has the option of requesting additional information from the drug sponsor if they are not completely convinced by the sponsor's results and conclusions. In such cases, the FDA sometimes uses advisory committees which can give advice on the review team's concerns. After the primary review has been successfully conducted, the supervisors of the individuals in the primary review team will carry out a secondary review. If the FDA feels the drug sponsor has been able to prove that the drug gives a clinical benefit, it will be granted marketing approval (Walsh, 1998, 66-67; FDA 2010[referred 7.7.2010]).

Since 1992, the FDA has been offering sponsors the opportunity of applying for a Priority Review which basically means that the time it takes for the review team to decide upon marketing approval is reduced to approximately six months (from the standard of ten months). However, Priority Review status is only given to drugs for serious, or also less serious, diseases that offer major advances in treatment or fill an unmet need in conditions where no adequate therapy exists. After receiving the request for Priority Review, the FDA has 45 days to decide whether a Priority or a Standard Review will be assigned for the drug in question (FDA 2010[referred 7.7.2010]).

In 2004, with the attempt to integrate the adoption of personalised medicine and to transform the way pharmaceutical products are developed, evaluated, manufactured and used, the FDA launched the Critical Path Initiative (CPI). The initiative encourages using highly technologic tools such as nanotechnology and process analytic technology for manufacturers, and for companies to develop biomarkers and new assays to be used as companion diagnostics. For instance, the anti-coagulant drug Warfarin has had dosing information added to its drug label due to collaborative research conducted through the CPI (CPI update, 2010 [referred 12.7.2010]).

Some PMDs are developed in parallel with a companion diagnostic, for instance while Genentech was developing its innovative drug Herceptin, indicated to treat HER2 overexpressing breast cancer, the company set up a partnership with Dako to develop a companion diagnostic product; HercepTest (Genentech, [referred 20.7.2010]). The drug was designed to target HER2 (Human Epidermal growth factor Receptor 2) genes in

HER2 positive breast cancer, in which the cancer cells have an abnormally high number of HER2 genes in cells which cause the fast spread of the cancer cells. Herceptin is a biological therapy which targets these genes in order to stop the cancer cells from growing (Herceptin, 2010 [referred 20.7.2010]). Hence, HercepTest was designed to detect the overexpression of HER2 protein in breast cancer patients and thus can be used to assist physicians in finding out whether Herceptin is a suitable therapeutic option for a particular breast cancer patient (DAKO, HercepTest [referred 20.7.2010]).

The regulations for medical devices in the US are fairly complex. Biomarker assays and other diagnostic products are classified into three groups by the FDA, depending on the indications for use and on the intended use. Furthermore, the classification is also based on the level of risk the device poses for patients with Class I including devices with the lowest risk and Class III those with the greatest risk. Class III medical devices require Premarket approval (PMA) from the FDA before being able to commercialise the product. The FDA describes Class III devices as products that "support or sustain human life, are of substantial importance in preventing impairment of human health, or which present a potential, unreasonable risk of illness or injury" (FDA, 2009 [referred 21.7.2010]).

For devices that belong to Class I or II (or exceptions in Class III) a 510(k) premarket notification submission is required to be filled to the FDA, instead of a PMA application. 510(k)'s purpose is to demonstrate that the device is at least as effective and safe as an already legally marketed device that does not require a PMA. The CBER is responsible for reviewing both PMAs and 510(k)s. The review process for PMAs takes approximately 180 days, whereas the review for 501(k) clearance takes only approximately 90 days. However, albeit these set regulations, some IVD tests do not require any FDA clearance. Such tests are called Laboratory Developed Tests (LDTs) and are developed in a specific laboratory which also performs all testing. The requirements for tests to fit in this category are for the laboratory to be CLIA validated (comply with Clinical Laboratory Improvement Amendments) and to develop and perform tests in the laboratory's own facilities only. The FDA has also compiled a list of Class I medical devices that do not require 510(k) clearance or PMA. Still, the

manufacturers of these products are required to register their establishments (FDA, 2009 [referred 21.7.2010]).

In the European market, there are two pathways for drugs to gain marketing authorisation: the centralised procedure of the European Medicines Evaluation Agency (EMEA) or the Mutual Recognition Procedure (MRP) with which the application is evaluated by regulatory authorities in any of the member countries of the European Union. The EMEA has been operating since 1995 and it is located in London, England (Walsh, 1998, 69).

The EMEA mainly evaluates novel and pioneering technologies. However, it does not evaluate pharmaceutical products directly but through two committees: medicinal products for human use (the CHMP) and medicinal products for rare diseases (the COMP). The CHMP coordinates the evaluation of all technologically advanced products for human use with excluding those treating rare diseases and the COMP evaluates orphan medicinal products which affect no more than 5 in 10,000 persons (Slater, 1997; Walsh 1998, 69-71). However, the EMEA does not distinguish new drug applications for biologicals and NMEs in the way as FDA does.

The EMEA has set up the Pharmacogenomics Working Party (PgWP) in 2005 which is a team of experts that provide recommendations to the CHMP on issues related to pharmacogenomics. The agency defines pharmacogenomics as "the study of the variability of the expression of individual genes relevant to disease susceptibility as well as drug response at cellular, tissue, individual or population level" (EMEA, PgWP mandate, 2009[online, referred 20.7.2010]). The group was established in order to be able to improve the understanding and adoption of the new technologies pharmacogenomics offer which can be used in developing innovative drugs such as PMDs.

After the drug sponsor has submitted their application for market approval in the centralised procedure, the EMEA has 10 days to give the initial appraisal stating whether the application is accepted for a review. If given a positive appraisal, the

application dossier will be sent to be appraised by a national authority in one of the member countries who will compile a report about the application. This report will be reviewed by the CHMP/COMP which issues a recommendation whether the drug should be approved or not. The review process should take approximately 210 days (Walsh 1998, 69-71). Drug sponsor can request for "accelerated approval" review which is similar to FDA's Priority Review. Accelerated approval can be granted to highly innovative drugs in order to speed up the review process which consequently brings the much needed drugs faster to the market.

The last stage of gaining market authorisation in the European Union is for the European Commission to review the report written by the national authority in question and the recommendations made by the CHMP/COMP and decide if the drug should be granted market approval. The European Commission has 90 days to finish this process hence the total time the market authorisation should take is 300 days. However, it can be considerably more if one of the bodies involved request for additional information from the drug sponsor (Walsh 1998, 69-71). All information of the assessment process is publically available and published as EPARs (European Public Assessment Reports) on the EMEA website.

The decentralised drug approval process, the Mutual Recognition Procedure, is used for products that do not qualify for an EMEA evaluation as well as for generic drugs and parallel imports. The Mutual Recognition Procedure issues a series of national authorisations based on the principle that EU Member States recognise each other's market authorisations. In order for a drug to be authorised, the drug sponsor must choose one of the member countries as its Reference Member State (RMS) of which national authority will conduct the initial marketing authorisation. The Mutual Recognition Facilitation Group will forward the initial authorisation to other Member States and if these Concerned Member States' (CMSs) national competent authorities approve it, the MRP is complete. The total duration of the MRP process is also the same 300 days as is the duration for the centralised procedure. Sometimes the CMSs refuse to grant authorisation even though the RMS would have granted marketing approval. In such cases, the CHMP arbitrates (Walsh 1998, 69-71).

For medical devices, it is required to apply for CE mark in order to be able to commercialise a medical device in any of the member states of the European Union. There are four types of CE marks which when granted prove that the manufacturer or the particular product has signed the declaration of conformity, that is, the device complies with the EU directives set for a particular product group. The categorisation of devices is based on the level of risk associated to the product and the EU directives concerning it. The body responsible for authorising CE marks is the European Committee for Standardisation together with national standards authorities. For IVD (In vitro diagnostic) products the Directive 98/79/EC of the European Parliament and of the Council applies (EU Directive 98/79/EC, 1998, [referred 21.7.2010]).

Once a drug has been granted marketing approval by the authority responsible for the market area, it can be launched. Launching a product means introducing the new product to the market and selling it in the market.

3. METHODOLOGY

The purpose of this study was to explore the regulatory environment of pharmaceutical industry in the US and EU, and also to analyse the impact it has on new product development of personalised medicine. To achieve this, the study was positioned as an exploratory research.

Exploratory research approaches allow the researcher to open up new areas of a given phenomenon or a new phenomenon entirely (McQuarrie, 2006, 6). Using the method of exploratory research in this study does not only able the identification of relationships between different actors, the regulators and drug sponsors, but can also help to explain patterns related to the process of drug development and commercialisation (Robson, 2002, 59). According to Saunders et al (2007,133), the three main methods of conducting exploratory research are searching relevant literature, interviewing experts of the field of interest and/or conducting focus group interviews.

As such data collection was conducted by means of desk research. This means collecting secondary data from various sources such as books, research articles, corporate reports, online databases and websites of pharmaceutical companies, and industry related organisations. This method was chosen due to the vast amount of public data available on the subject of interest, such as case studies on regulations related to the process of developing and marketing drugs, and data on specific Personalised Medicine Drugs (PMDs) from the drug developing companies' websites and annual reports.

As part of my studies in the Turku University of Applied Sciences, I did my internship for a company called Diaceutics which is a consulting firm specialised in personalised medicine. One of the research projects I assisted with was focused on the drugs I also chose to use in my "Case of Personalised Medicine" for this study. The drugs were chosen because they all are considered as PMDs and all have diagnostic tests identifying particular biomarkers, which can be used to assist with safety and/or efficacy issues related to the medicinal therapy.

In this study, the desk research data obtained was mainly statistical data, case studies and corporate reports. Data on the marketing authorisations was found from the websites of the FDA and EMEA, whereas data on the drugs and their development timeline was available on the drug developer's (or in some cases the company entitled to market the product) websites. For some drugs, such as Iressa and Herceptin, a whole website has been established with the attempt to increase the awareness and knowledge of patients and healthcare professionals on the drug.

Generally, any data acquired without fieldwork is considered to be conducted by a desk research (Hague & Hague, 2004, 32-47). Google News Archive proved to be a very useful source of information. The archive consists of a large number of news articles that have been published in various newspapers or magazines all over the world and can be traced back several years, even decades. I used it for instance to obtain data on the drug and test launch dates in cases where the drug/test sponsor's website did not provide that information. Annual reports of pharmaceutical and diagnostics companies were used in addition to gather information on specific drugs and tests. Also, articles from magazines specialised in the pharmaceutical industry and biotechnology, were good sources of data offering the latest updates of products, technologies and changes in the regulatory environment.

Desk research can be used as the sole means of data collection, like in this study, but also as part of data collection which includes the aspect of primary research. In such a case, desk research would be used to collect background information which would point out direction for the primary research or provide additional information (Birn, 2004, 19). However, collection of primary data for this study was not necessary due to the nature of this research.

The data was analysed by using content analysis. Stone et al (1966, 5) describe content analysis as "any research technique for making inferences by systematically and objectively identifying specified characteristics within text". This approach was also accepted by Krippendorff (2004, 18) who defines content analysis as "a research technique for making replicable and valid inferences from texts, or other meaningful

matter, to the contexts of their use". By other meaningful matter he refers to a whole variety of sources which should be considered: maps, sounds, works of art, images, symbols and numerical records. Furthermore, content analysis is empirically grounded and exploratory in process, combining mechanical and interpretative components (Krippendorff, 1980).

Within the past decades, there has also been definitions varying quite extensively from Krippendorff's and Stone et al's ones. For instance, Berelson (1954, 489) related content analysis only to analyse the content of communication, providing a much narrower concept than Krippendorff and Stone et al after him. In respect to this study, Krippendorff's approach is most consistent with the type of data used.

Thus, the analysis was conducted by dividing the gathered secondary data into categories from which it was in an interpretative manner decided which of the categories are most significant to the research objectives. In practise, the drugs chosen for the case study were segmented into categories based on the relationship the drug and test had in the development process and the importance the regulatory bodies have based on the tests. The time lapses were investigated in days for all of the objectives except for the time between drug launch and test launch which was measured in months. This was done since the exact launch dates for most of the tests were not available, but data was available for the month and year of the launch in most cases. The process of the analysis was reciprocal throughout and aimed to provide increased understanding and new findings of the process drugs go through before being commercialised.

There were also some limitations to this study which were mostly related to the availability of data. Finding exact information on launch dates was difficult due to the complex nature of test regulations in the US and the fact that in Europe, drugs can be launched simultaneously in various countries or just in one country which consequently makes it difficult to find exact information. These limitations made the data collection and analysis more time consuming and complex. The limitations mentioned may also have affected the outcome of the research since the smaller the sample, the bigger the

possibility of errors. In this case, errors could mean generalising the phenomenon based on a relatively small number of examples.

4. THE CASE OF PERSONALISED MEDICINES

In this study ten personalised medicine drugs (PMDs) were analysed with the focus on the impact regulatory environments have on the drug approval and launch processes (Table 1). The selection criteria for the drugs were the use of pharmacogenomics (PGx) either in the development process of the drug or after the initial drug development to enhance its safety and/or efficacy, and also for the drug to have diagnostic test(s) available to identify specific biomarkers. The biomarker assays for the pharmaceuticals are used to assist with safety and/or efficacy issues related to the medicinal therapy.

Table 1 Drugs and Indications

Drug Name	Drug Sponsor	Indicated to Treat
Herceptin	Genentech	Cancer
Erbitux	ImClone	Cancer
Selzentry/Celsentri	Pfizer	HIV
Vectibix	Amgen	Cancer
Iressa	AstraZeneca	Cancer
Ziagen	Glaxo Wellcome	HIV
Tarceva	Osi	Cancer
Tamoxifen	AstraZeneca	Cancer
Coumadin	BMS	Coagulation
Gleevec/Glivec	Novartis	Cancer

Seven PMDs chosen for the case study are used to treat different types of cancer: Herceptin, Erbitux, Vectibix, Iressa, Tarceva, Tamoxifen and Gleevec. Two of the drugs included in the analysis have been developed to treat HIV infection; Selzentry and Ziagen, and one, Coumadin to treat blood coagulation. All of the drugs are described in more detail in the following chapter.

4.1. Product Descriptions

Herceptin is a biological drug indicated for the treatment of HER2 overexpressing breast cancer, and was developed by Genentech. Biological drugs are derived from biological sources (living organisms) and can be either protein- or nucleic acid- based, whereas small-molecule drugs (SMDs) are chemical entities as described in Chapter 2.3.1. Herceptin's active ingredient is trastuzumab.

Erbitux is also a biological oncology drug like Herceptin and was developed by ImClone. The drug's active ingredient is cetuximab, and it is indicated to treat head and neck cancer, and also EGFR expressing metastatic colorectal cancer with the exception of patients with KRAS mutations in their tumors in codon 12 or 13. Amgen's drug Vectibix is used for the same indication in colorectal cancer. EGFR and KRAS are genomic biomarkers that have been detected to influence the efficacy of Erbitux and Vectibix in specific patient populations. Vectibix is the third biological drug analysed in this study and its active ingredient is panitumumab.

Selzentry, developed by Pfizer, differs from the drugs mentioned above quite extensively. This is due to the fact that it is neither an oncology nor a biological drug but an SMD antiviral. Antivirals are drugs that are used to treat viral infections. The drug is marketed in Europe under the name of Celsentri, and is specifically indicated for treatment of adults infected with CCR5-tropic HIV infection. Its active ingredient is maraviroc. Another SMD antiviral included in this study was Glaxo Wellcome's Ziagen which active ingredient is abacavir. Ziagen is used for the treatment of HIV infection.

Iressa and Tarceva are both SMDs indicated for patients with locally advanced or metastatic non-small cell lung cancer and were developed by AstraZeneca and Osi Pharmaceuticals respectively. Iressa's active ingredient is gefitinib and Tarceva's erlotinib.

Tamoxifen is an oncology drug which was developed by AstraZeneca to treat metastatic breast cancer. The drug was already approved by the FDA in 1977. It was sold under

the brand name Nolvadex (tamoxifen is the name of the active ingredient) until 2006, when AstraZeneca pulled the drug out of the market due to increased generic competition after the patent of the drug had expired.

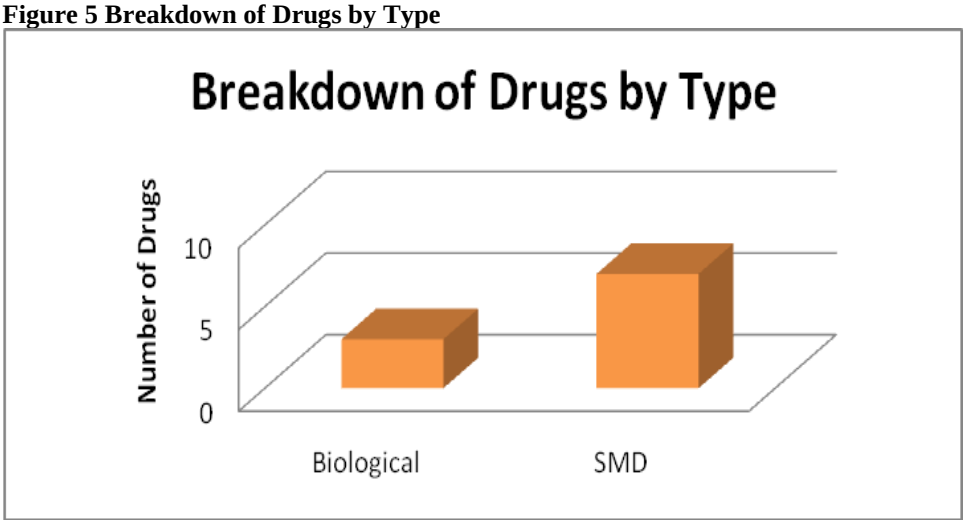
Gleevec is also an SMD oncology drug and its active ingredient is imatinib. The drug was developed by Novartis and is marketed as Glivec in the European market. The drug is indicated for the treatment of patients with Philadelphia chromosome positive myeloid leukemia (Ph+ CML) and also for patients with Kit positive gastrointestinal stromal tumors (GIST). Coumadin is the second older drug included in this study in addition to Tamoxifen; the FDA approved it already in 1954. The anticoagulant was developed by Bristol Myers Squibb and its active ingredient is warfarin. The drug is indicated for prevention and/or treatment of venous thrombosis and its extension, and pulmonary embolism (Drugs @ FDA [referred 26.7.2010]). Anticoagulants are generally used to prevent blood from clotting in veins. Table 2 lists all of the drugs used in this case study with their active ingredients.

Table 2 Drugs and Active Ingredients

Drug's Marketing Name	Active Ingredient
Herceptin	trastuzumab
Erbitux	cetuximab
Selzentry/Celsentri	maraviroc
Vectibix	panitumumab
Iressa	gefitinib
Ziagen	abacavir
Tarceva	erlotinib
Tamoxifen	tamoxifen
Coumadin	warfarin
Gleevec/ Glivec	imatinib

Out of the ten drugs chosen for this case, three happened to be biological drugs; Herceptin, Erbitux and Vectibix. The rest of the drugs introduced above are SMDs. Figure 5 shows the distribution of Biological drugs and Small-Molecule Drugs used in the analysis.

Figure 5 Breakdown of Drugs by Type



The drugs were divided in three groups based on their innovativeness and the extent to which companion diagnostics are part of the medicinal therapy (Table 3). The level of innovativeness was assumed to be higher for drugs that have been developed parallel to a companion diagnostic. The reasoning behind this assumption is based on the high level of scientific and technological input in the drug discovery and development process required for developing targeted therapies. That is, matching the right patients with the most beneficial medicinal therapy.

The criteria for a drug to be included in the group of Type A drugs was for the drug to be developed in parallel with a diagnostic test. Herceptin, Erbitux and Selzentry, were all developed in parallel with a companion diagnostic. The tests are required to be used prior therapy in order to establish whether the patient is likely to respond and thus benefit from the drug. The FDA and the EMEA have both stated that biomarker testing is mandatory for Herceptin and Erbitux, yet only the FDA has placed Selzentry under the mandatory biomarker testing status. This difference in the importance the two regulators have placed on a specific test can be caused by a variety of reasons. For instance, the differences in the procedures how medical devices are categorised and regulated in different markets can result in disparities in the global market.

For a drug to be categorised as Type B, the test for the drug must have been declared mandatory by the EMEA and developed prior or after the drug in order to improve the

safety or efficacy of the medicinal therapy. The drugs that met these criteria were Vectibix, Iressa, Tarceva and Ziagen, all of which have mandatory biomarker testing in Europe but not in the US. The test for Ziagen is not to assist with efficacy of the drug, as the tests for the other Type B drugs, but to detect whether a patient is hypersensitive to the active ingredient of the drug, abacavir. Thus, the test is used to assist physicians making clinical decisions with the emphasis on the safety of the drug.

The Type C drugs, Tamoxifen, Gleevec and Coumadin, are drugs for which a valid genomic biomarker has been identified, yet the biomarker testing is only recommended by the FDA and EMEA, not mandatory. For testing to be only recommended by the FDA and EMEA is usually due to insufficient clinical data proving a substantial benefit from using the product. The tests developed to be used with Coumadin are to provide information on how the patient metabolises the drug, which assists physicians when deciding upon a suitable dosage of the drug for individual patients. The tests for Tamoxifen and Gleevec have been developed to assist predicting efficacy of the drug in specific patients. Table 3 lists the drugs according to the Types described above.

Table 3 Drugs Categorised According to Type

Drug Type	Type Description	Products
Type A	• The drug was developed in parallel with a companion diagnostic • The testing is declared mandatory by the FDA and/or the EMEA	• Herceptin • Erbitux • Selzentry/Celsentri
Type B	• There must be an available biomarker test which has been developed to improve the efficacy or safety of the drug • The testing is declared mandatory by the FDA and/or the EMEA	• Vectibix • Iressa • Ziagen • Tarceva

Type C	• Biomarker test(s) available for the drug but testing is only recommended by the FDA and/or the EMEA	• Tamoxifen • Coumadin • Gleevec/Glivec

There are differences how significant the regulatory agencies find the usage of diagnostic devices in combination to pharmaceuticals. For example, out of the ten drugs the FDA has declared biomarker testing mandatory for three drugs; Herceptin, Erbitux and Selzentry, whereas the EMEA requires testing for six; Herceptin, Erbitux, Ziagen, Tarceva, Vectibix and Iressa.

4.2. Application to Marketing Approval

In order for a drug to be commercialised, it needs to be approved by the regulatory authority responsible for the market area. In the US, the FDA reviews all drugs and already in the application submission stage the drugs are divided in either biological drugs or small molecule drugs (SMDs). Drug sponsors hoping to get a biological drug approved must submit a Biologics Licence Application (BLA) to the FDA and if marketing approval is granted, the drug sponsor is free to launch the product in the US market. For SMDs the application requesting marketing approval is called New Drug Application (NDA).

Table 4 outlines the type of application drug sponsors submitted to the FDA with the desire to be granted marketing approval. Herceptin, Erbitux and Vectibix are biological drugs hence the BLAs. The rest of the drug sponsors submitted NDAs due to the fact that the drugs are SMDs. All of the ten drugs, except for Tamoxifen and Coumadin went through the priority review process. The priority review process, discussed in Chapter 2.3.2, is an accelerated version of the standard review process and can be applied for innovative drugs that fall into specific categories the FDA has established. However, the reason why Tamoxifen and Coumadin did not go through the priority review process may not have anything to do with their level of innovativeness, but only

with the changes happened in the regulatory process within the past decades. That is, Tamoxifen was already approved in 1977 and Coumadin in 1954, and the priority review option was not introduced until 1992.

Table 4 FDA Review

DRUG	Type of Application	Type of Review
Herceptin (Genentech)	BLA	Priority
Erbitux (ImClone)	BLA	Priority
Selzentry/Celsentri (Pfizer)	NDA	Priority
Vectibix (Amgen)	BLA	Priority
Iressa (AstraZeneca)	NDA	Priority
Ziagen (Glaxo Wellcome)	NDA	Priority
Tarceva (Osi)	NDA	Priority
Tamoxifen (AstraZeneca)	NDA	Standard
Coumadin (BMS)	NDA	Standard
Gleevec/ Glivec (Novartis)	NDA	Priority

The EMEA does not distinguish marketing applications for biologicals and SMDs in the way the FDA does. This is due to the differences in the procedures it takes for the regulatory authorities to grant marketing approvals. As described in Chapter 2.3.2, in Europe, there are two pathways for drug sponsors to apply for marketing approval, either the centralised procedure, or the Mutual Recognition Procedure (MRP).

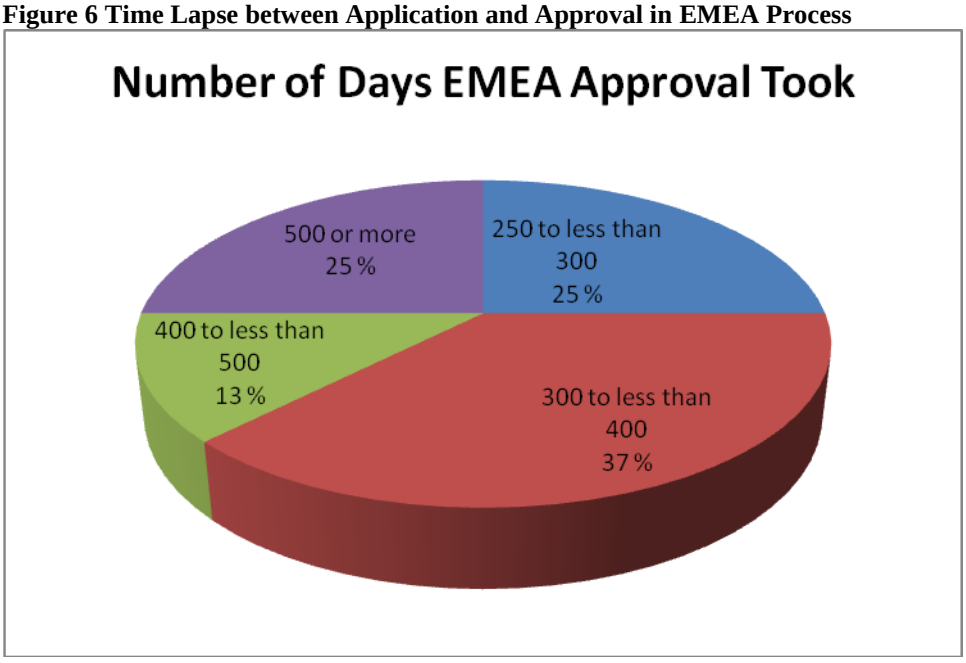
Depending on the type of process chosen, the authority responsible assigns the application to the review board specialised either in biological drugs or SMDs. A similarity the EMEA process bears to the FDA process is the different types of reviews, in terms of duration of the review, available. The EMEA calls the faster review process as the Accelerated Approval Process.

All of the ten personalised medicine drugs went through the centralised review in the European Union. Selzentry was the only drug reviewed on the accelerated route. Another exceptional approval granted by the EMEA was for Gleevec which was given

Orphan drug status in the beginning of the approval process. To be categorised as an orphan drug, often speeds up the review process the same way as does the accelerated review. Since Orphan drugs are designed to treat a specific disease or medical condition that affects only a small patient population, they are often pushed to the market extremely quickly. This is because they are considered to offer major advances in treatment or fill an unmet need in conditions where no adequate therapy exists.

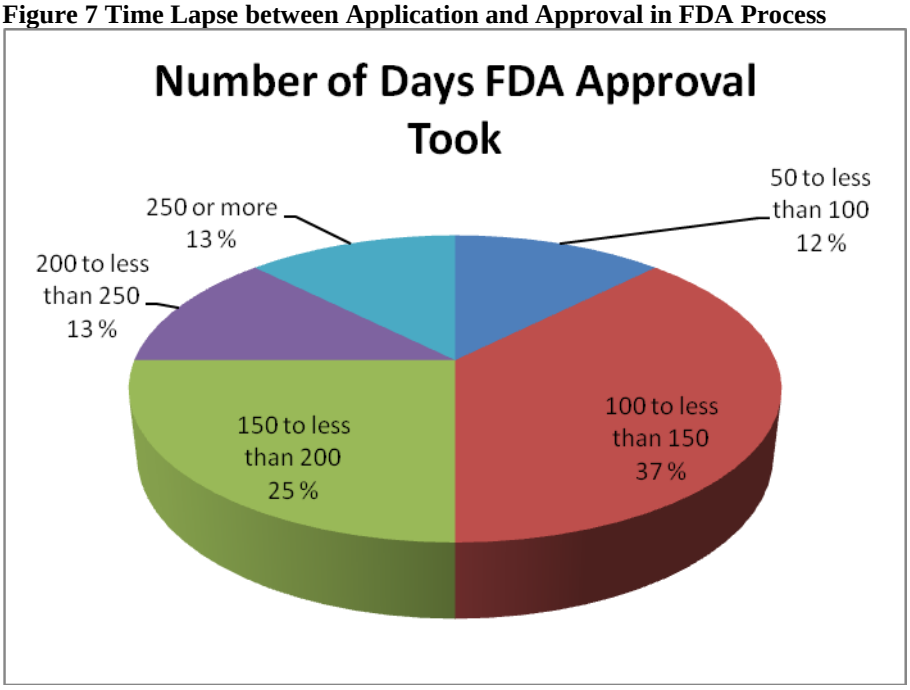
Out of the ten drugs analysed in this study, data on the timeline between submitting the marketing approval application and gaining marketing approval was available for eight drugs. The data was unattainable for Tamoxifen and Coumadin. Figure 6 describes the distribution of the length the approval process took in Europe. The EMEA approval took between 300 to 400 days for 37 percent of the drugs. The duration of the approval process for 13 percent of the drugs was between 400 and 499 days, and for the remaining drugs the duration of the review was either between 250 and 299 days, or more than 500 days.

Figure 6 Time Lapse between Application and Approval in EMEA Process



In comparison to this, Figure 7 shows the distribution of days the process took for the FDA. The number of days the FDA process took is considerably smaller than the number of days the EMEA process took. For only 13 percent of the drugs reviewed by the FDA the process took 250 days or more, whereas the EMEA review process took over 250 days for all of the drugs. For 12 percent of the drugs the number of days between submitting application to be granted marketing approval and actually gaining the approval was 50 to 99 days. For 37 percent of the drugs reviewed by the FDA, the process took between 100 and 149 days.

Figure 7 Time Lapse between Application and Approval in FDA Process



Type A Drugs

Examining the time lapse between submitting application and being granted marketing approval, for Type A drugs specifically, the EMEA approval process took the longest for Herceptin. The process lasted 583 days. For Selzentry the duration of the process was 230 days and for Erbitux 182 days. On average the number of days it took for EMEA to approve a new drug was 405 days which makes Herceptin the only drug from this group to excel this.

For the FDA it took 230 days to grant Selzentry marketing approval and 182 days for Erbitux. Herceptin was the quickest to be approved by the US agency with only 144 days which is below the FDA average of 166 days. Thus, the rank of the drugs to be approved by the FDA in terms of fastness is reverse in comparison with EMEA's. Between the two regulators, the largest difference in the time lapse of granting approval was for Herceptin, for which it took 419 more days for EMEA to approve the drug in comparison with the FDA.

Type B Drugs

In this category, Vectibix and Iressa were the drugs that exceeded the EMEA average of 405 days to be granted marketing approval. For Vectibix the duration of the process was 583 days and for Iressa 427 days. Tarceva and Iressa stayed below the average with the process lasting 388 days and 373 days respectively.

For the FDA it took the longest to review Iressa with the process taking 276 days. The duration of the approval process for both Iressa and Ziagen, took longer than the FDA average of 166 days with the time lapse between application submission and gaining marketing approval being 176 days for Ziagen, and 276 days for Iressa as mentioned. Tarceva was the quickest to be granted marketing approval by the FDA with the process taking only 112 days. The FDA approval process took 138 days for Vectibix, resulting Vectibix being the drug in this group with the biggest difference in the time lapse of application submission and gaining marketing approval between the European and US regulators. It took EMEA 445 days longer to grant Vectibix marketing approval than it took the FDA to do the same.

Type C Drugs

The only drug belonging to Type C that data was available for was Gleevec. The drug was approved rather rapidly in both markets with the EMEA process lasting 255 days

and the FDA 72 days. All of the drugs and the time lapse between application submission and approval can be seen in table 5 below.

Table 5 Time Lapse between Application Submission and Marketing Approval

Type	Drug Name	Time lapse EMEA (days)	Time lapse FDA (days)	Difference between EMEA and FDA (days)
A	**Herceptin (Genentech)**	563	144	**419**
A	**Erbitux (ImClone)**	364	182	**182**
A	**Selzentry (Pfizer)**	285	230	**55**
B	**Vectibix (Amgen)**	583	138	**445**
B	**Iressa (AstraZeneca)**	427	276	**151**
B	**Ziagen (Glaxo Wellcome)**	373	176	**197**
B	**Tarceva (Osi)**	388	112	**276**
C	**Tamoxifen (AstraZeneca)**	n/a	n/a	**n/a**
C	**Coumadin (BMS)**	n/a	n/a	**n/a**
C	**Gleevec/Glivec (Novartis)**	255	72	**183**
	Mean	405	166	**239**
	Median	381	160	**190**

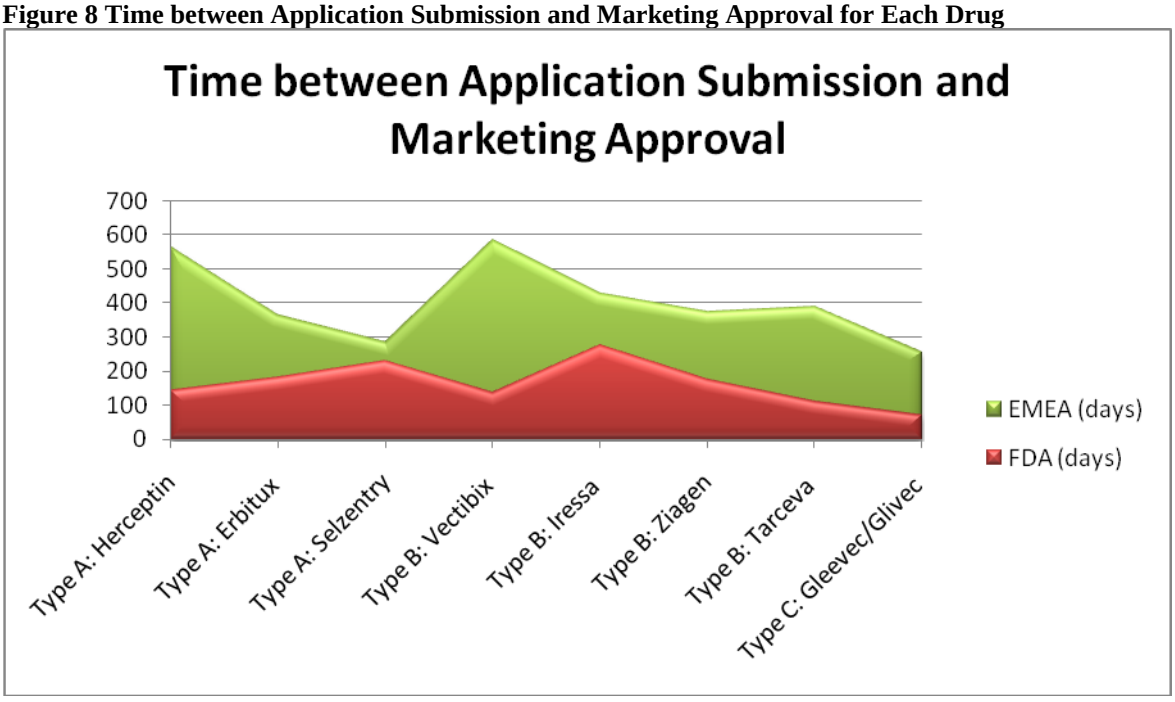
4.2.1. Summary

It seems that the FDA process for granting marketing approvals is considerably quicker than the EMEA process. Gleevec was the fastest drug to be approved by both the FDA and the EMEA (Figure 6). The time lapse between submitting application and granting

marketing approval was only 72 days for the FDA and 255 days for the EMEA. However, it must be noted that there was quite a significant difference between the two regulators when comparing the duration of the process for Gleevec; the process took 183 days longer for the European agency than the US agency.

On average, the difference between the timeline of the reviews conducted by the EMEA and the FDA was 239 days. The largest differences in the time lapse between the two regulators granting marketing approval were for Herceptin and Vectibix, both of which are biological drugs. The smallest differences in the time lapse between the two markets were for Selzentry and Gleevec, both of which were accepted to be reviewed on the faster approval route in the US and the EU. The EMEA process for two out of the three biological drugs, took more than the average of 405 days. These drugs were Herceptin and Vectibix. For biological drugs reviewed by the FDA, only Erbitux stayed above the FDA average of 166 days, with the process lasting 182 days.

Figure 8 Time between Application Submission and Marketing Approval for Each Drug



Both Selzentry and Gleevec were given special review status by the EMEA which is in consistence with the two drugs being approved significantly faster than the rest of the drugs. All of the drugs approved by the FDA were given the priority review status

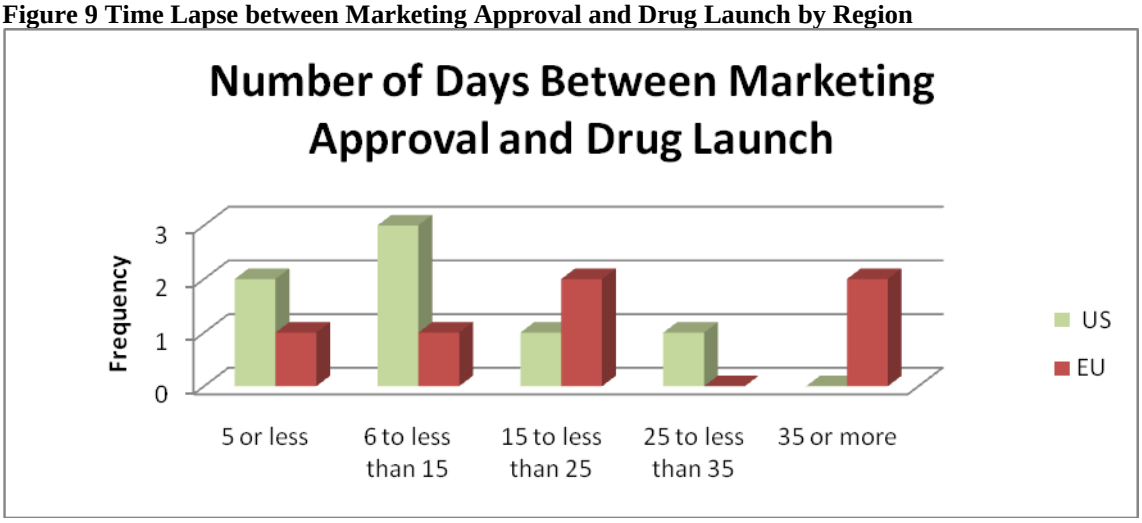
which explains the more modest differences in the timeline between all drugs in comparison to EMEA.

4.3. Marketing Approval to Drug Launch

Part of my objective in this study was to examine the time lapse from the moment a new pharmaceutical has been granted marketing approval until it is launched. Examining the time lapse between the stages of having been granted marketing approval and for the drug to be launched is more straightforward in the US market than in the European market. In Europe, once a drug is approved, it can be either launched in one country or in many countries simultaneously. Hence, for this study the United Kingdom (UK) has been chosen to represent the launch of pharmaceuticals in Europe. The UK was chosen for two reasons: the EMEA is located in the UK and the pharmaceutical market in the UK is one of the major European markets alongside Italy, France, Germany and Spain.
The data for the time lapse between gaining marketing approval and launching a new pharmaceutical was available for seven of the drugs in the US market and for six in the European market. The data was unattainable for Tamoxifen, Coumadin and Ziagen in both markets and for Herceptin in the European market.

For five out of seven drugs the time lapse between gaining marketing approval and launching the drug was less than 15 days in the US, whereas in the EU, for four out of six drugs, the number of days between approval and launch was over 15 days. It must be also noted that for none of the drugs examined in this case did the US launch take more than 35 days which could not be said of the European launches (See Figure 9). For two of the drugs the time lapse between approval and launch was over 35 days.

Figure 9 Time Lapse between Marketing Approval and Drug Launch by Region



This difference can be caused by a variety of reasons. The US pharmaceutical market is more unite than the European market; even though member countries of the European Union have joint EU directives and regulations to follow, all countries have their own legislations which impact markets. Another reason could be the strategic approaches pharmaceutical companies follow when launching new products. For instance they might have one strategy for the US market but will need various different strategies for the European market since there are vast differences between the European countries. Thus, different approaches for each country might be required.

On average, it took 13 days for drug sponsors to launch the newly approved pharmaceutical in the US market. In the European market the average was 27 days. Table 6 shows the number of days launching a new product after gaining marketing approval took for each of the drugs.

Table 6 Time Lapse between Gaining Marketing Approval and Drug Launch

Type	DRUG	USA (days)	EU (days)
A	Herceptin	10	n/a
A	Erbitux	13	23
A	Selzentry/Celsentri	34	63
B	Vectibix	16	51
B	Iressa	14	8
B	Ziagen	n/a	n/a
B	Tarceva	4	3

C	**Tamoxifen**	n/a	n/a
C	**Coumadin**	n/a	n/a
C	**Gleevec/Glivec**	1	16
	Mean	**13**	**27**

Type A Drugs

For Herceptin, the number of days between gaining marketing approval and launching the new pharmaceutical was 10 days in the US market. Data on its European launch was not available. For Erbitux, the time lapse was 23 days in the European market and 13 days in the US market. In both of the markets, it took the longest for Selzentry to be launched after gaining marketing approval with the time lapse being 63 days in the EU and 34 days in the US. Thus, for both of the drugs data was available for both markets, the launching took longer in the European market. Selzentry was the only drug from this group for which the time lapse in both markets was larger than the EU average of 27 days and US average of 13 days.

Type B Drugs

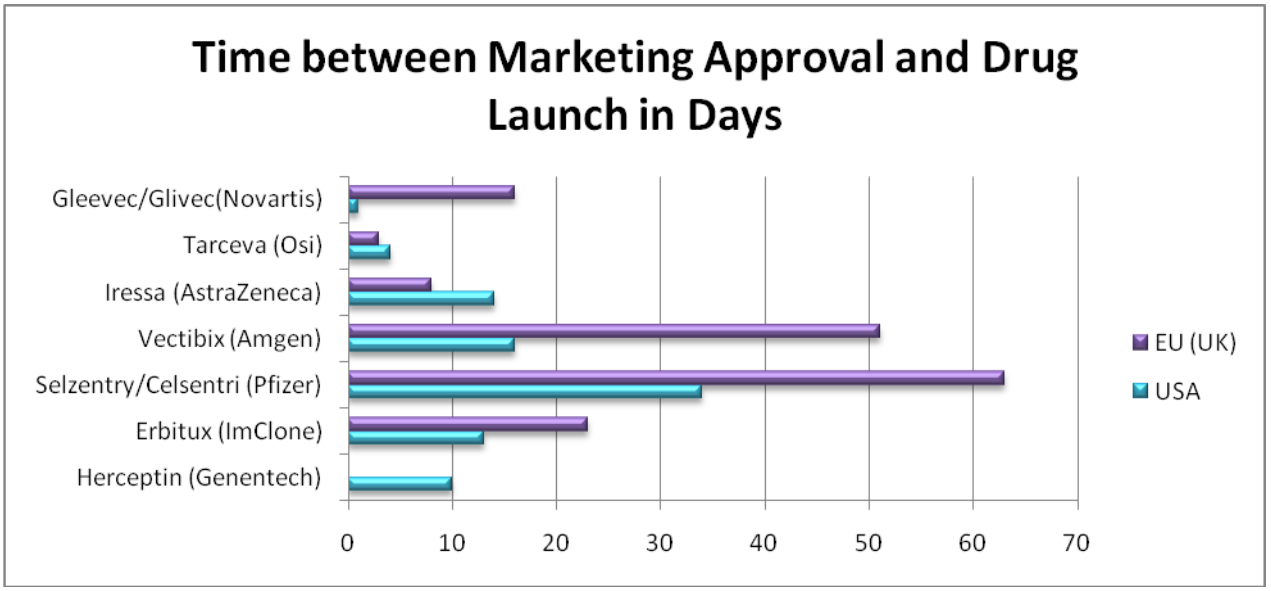
The time lapse between marketing approval and launch for Tarceva was almost the same in the EU and US markets; 3 days in the EU and 4 days in the US. For Iressa, the launching also took less time in the EU than in the US with the figures being 8 and 14 respectively. The number of days between approval and launch was considerably longer for Vectibix in both markets, it took 51 days for the drug to be available in the EU market and 16 days in the US market. Thus, the time lapse for launching Vectibix exceeded both the EU average of 27 days and US average of 13 days. Also, for Iressa launching took a day longer than the US average.

Type C Drugs

Data was only available for Gleevec in this group. The time lapse between marketing approval and launch was 16 days in the EU and 1 day in the US, both of which are well

below the EU and US averages. Figure 10 shows the time lapse between gaining marketing approval and new product launch for each of the drugs.

Figure 10 Time Lapse between Marketing Approval and Drug Launch for Each Drug



4.3.1. Summary

It appears that on average the drugs are brought to the market faster in the US than in the EU. The drugs launched the quickest in the US were Gleevec with only 1 day after gaining marketing approval, and Tarceva with only 4 days. In the EU, the drugs analysed for the same indicator were Tarceva with 3 days and Iressa with 8 days. The time difference between US and EU launch for Tarceva was only one day which stands out from the rest of the drugs quite significantly. For instance, the next drug with the smallest difference in days was Iressa with 6 days.

The drugs that took the longest to be launched in both markets were Selzentry and Vectibix. Selzentry's launch took 34 days in the US and almost twice as long in the EU with 63 days. Vectibix was the second drug for which launch after gaining marketing approval took the longest with 16 days in the US and 51 days in the EU. However, the gap between the US launch of Vectibix and Iressa, which would have been the next in line with the most days launching the product took, was not as remarkable as the gap

between the EU launch of Vectibix and Erbitux, with the number of days being 16 and 13; and 51 and 23 respectively.

It can be speculated that the differences in market environments in the US and EU result in pharmaceuticals being launched faster in the US market. In addition, the nature of the product may impact in the fastness the product is pushed to the market. For instance, the orphan drug Gleevec was commercialised within a day after gaining approval in the US market.

4.4. Drug Launch to Test Launch

The last part of my objective was to analyse the time lapse between the initial drug launch and launching a biomarker test for the drug. Some of the biomarker tests were launched in a similar way as pharmaceuticals; first applying and gaining marketing approval, after which commercialising the product is legal. However, since the regulatory environment, described in further detail in Chapter 2.3.2, is rather complex for medical devices, it must be mentioned here that some of the tests cannot be launched for commercial purposes, depending on the classification of the product. These tests are the Laboratory Developed Tests (LDTs) which can only be used in the laboratories where they were developed and hence not sold as test kits to be used elsewhere.

For some of the drugs a number of tests are available which is why for this objective the first test commercialised suitable for detecting the biomarker appropriate for a particular drug was chosen (Appendix 1). For some of the drugs the same tests can be used since they have the same target protein in the tumours, located in the same part of the body. For instance, the same test, Dako EGFR PharmDx Kit, can be used to test for EGFR expression in tumours for patients with colorectal cancer in order to establish whether the patients are likely to benefit from Erbitux and Vectibix therapies. It has also been discovered that patients with KRAS gene mutations are unlikely to respond to Erbitux

and Vectibix which is the reason there are two separate tests, EGFR and KRAS, for these drugs.

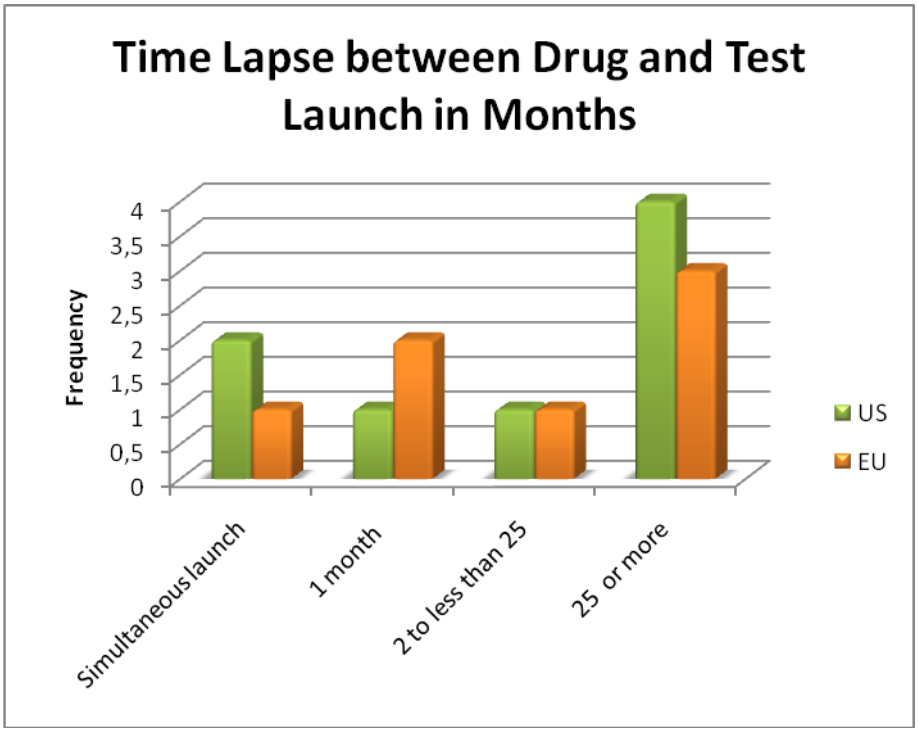
However, there is an extensive difference in how the US market and the European market regulate KRAS testing. In Europe, there are KRAS tests such as the DxS TheraScreen KRAS which is CE-marked and commercially available, whereas in the US there are no FDA regulated KRAS tests but only LDTs. LDTs cannot be launched in the device market but only be used in the laboratories that have developed them. Thus, in the analysis of the time lapse between drug and test launch, both of the biomarkers have been taken into account even though no data is available on KRAS test launches in the US market for obvious reasons. Table 7 lists the drugs with their biomarkers and tests used in the analysis.

Table 7 Drugs and Tests Based on Biomarkers

Drug Name	Valid Genomic Biomarker	Diagnostic Test for the drug available in the US market	Diagnostic Test for the drug available in the EU market
Type A			
• **Herceptin**	• HER2+	• HercepTest	• HercepTest
• **Erbitux**	• EGFR+/KRAS	• Dako EGFR PharmDx/KRAS LDTs	• Dako EGFR PharmDx/ Dxs TheraScreen KRAS
• **Selzentry/ Celsentri**	• CCR5	• Monogram Trofile	• Monogram Trofile
Type B			
• **Vectibix**	• EGFR+/KRAS	• Dako EGFR PharmDx/KRAS LDTs	• Dako EGFR PharmDx/ DxS TheraScreen KRAS
• **Iressa**	• EGFR –	• Genzyme EGFR	• DxS TheraScreen EGFR
• **Tarceva**	• EGFR-	• Genzyme EGFR	• DxS TheraScreen EGFR
• **Ziagen**	• HLA-B*5701	• LabCorp HLA-B5701	• Delphic HLA-B5701
Type C			
• **Tamoxifen**	• CYP2D6 variants	• Roche Amplichip	• Roche Amplichip
• **Coumadin**	• CYP2C9 & VKORC1 Variants	• PGx Predict Warfarin	• n/a
• **Gleevec/ Glivec**	• C-Kit	• Dako C-Kit PharmDx	• Dako C-Kit PharmDx

To examine the time lapse between drug launch and its biomarker test launch data was available for eight drugs in the US market and seven drugs in the EU market. The drugs data was unattainable for were Tamoxifen and Coumadin in both markets and Ziagen in the European market. The time between drug launch and test launch was measured in months since the exact launch dates for most of the tests were not available, but data of the month and year of the launch in most cases could be found. It can be seen from Figure 11 that in the US, two drugs were launched the same month as their tests. These drugs were Herceptin and Erbitux. Figure 11 shows the time lapse between drug launches and test launches in months.

Figure 11 Time Lapse between Drug and Test Launch by Region



In Europe, one drug was launched the same month as its test which was Vectibix. The drugs that had a test launched a month before or after the drug were Herceptin in the EU and Selzentry in both markets. In the US and the EU, for one drug it took between 2 and 24 months for the test to be available. This drug was Tarceva. For the rest of the drugs, the time lapse between the drug being launched and the test being launched (in either order) was over 25 months.

Type A Drugs

Herceptin, Erbitux and Selzentry were all launched either on the same month as the companion diagnostic tests or a month after the test launch in the US market. This was expected since the products had been co-developed. In the European market the findings appear similar with the exception of the KRAS testing for Erbitux which was available 42 months after the launch of the drug. This difference can be explained with the fact that the drug's companion diagnostic was the Dako EGFR PharmDx Kit, and the KRAS testing was developed afterwards. Thus, it can be said that both in the US and in the EU all Type A drugs were launched within a month from their companion diagnostics.

Type B Drugs

Vectibix stands out considerably from the rest of the drugs since in the US, the EGFR test was launched almost 3 years earlier than the drug, whereas the KRAS test was launched at the same time as the European launch of the drug. As mentioned earlier, the same EGFR test can be used for both Erbitux and Vectibix and since Vectibix was launched 32 months after Erbitux, by this time the KRAS test had been developed. The DxS TheraScreen KRAS test had been CE-marked and launched in Europe the same month as Vectibix was launched.

The same biomarker tests can be used for Tarceva and Iressa. Iressa was launched before Tarceva in the US which is why the time lapse before the test was available was only 10 months for Tarceva and 28 months for Iressa. However, in the European market, the order for the launch of these two drugs was reverse. Thus, the number of months between drug launch and test launch in the European market was 19 for Tarceva. In Iressa's case, the appropriate test had already been in the market 27 months before the drug (Table 8).

The drug for which the time lapse between drug launch and test launch was the longest was Ziagen, with 71 months the drug being on the US market before the test. The nature

of the test can explain this. The HLA-B*5701 biomarker test is designed to detect those patients who are hypersensitive to Ziagen and thus unsuitable to be treated with the medicine. Often such issues cannot be detected in the initial clinical trials but after the drug has already been in the market. Moreover, a specific need for a diagnostic product was developed and after the test is commercialised, it can be used to increase safety of using the specific drug.

Type C Drugs

The only drug in this category for which data was available for was Gleevec. The biomarker test for Gleevec was launched 33 months after the drug's launch in the European market, and 49 months after the drug's US launch.

Table 8 Time Lapse between Drug Launch and Test Launch in Months

Drug	Name of Tests launched in the US	Name of Tests launched in the EU	Months between drug and test launch in US	Months between drug and test launch in EU
Herceptin	HercepTest	HercepTest	0	-1
Erbitux	Dakocytomation EGFR pharmDx test kit	Dakocytomation EGFR pharmDx test kit	0	n/a
	KRAS Laboratory developed tests	DxS TheraScreen KRAS	n/a	42
Selzentry/ Celsentri	Monogram Trofile	Monogram Trofile	-1	-1
Vectibix	Dakocytomation EGFR pharmDx test kit	Dakocytomation EGFR pharmDx test kit	-32	0
	KRAS Laboratory developed tests	DxS TheraScreen KRAS	n/a	0
Iressa	Genzyme EGFR	DxS TheraScreen EGFR	28	-27
Ziagen	Labcorp HLA B5701	Delphic HLA B5701	71	n/a
Tarceva	Genzyme EGFR	DxS TheraScreen EGFR	10	19
Tamoxifen	Roche Amplichip	Roche Amplichip	n/a	n/a

Coumadin	PGx Predict Warfarin	n/a	n/a	n/a
Gleevec/Glivec	DakoCytomation C-Kit PharmDx	DakoCytomation C-Kit PharmDx	49	33
Mean			**16**	**8**

4.4.1. Summary

It can be seen that for all the biological drugs; Herceptin, Erbitux and Vectibix, a test was available straight after the drug was launched. For all Type A drugs, tests were commercialised either a month before or simultaneously with the drug. In general, the time lapse between launching the drug and test was longer for Type B and C drugs.

Table 8 shows clearly that the timeline between the drug launch and the test launch was on average shorter in the EU than in the US. The negative numbers depict the number of months the test was launched before the drug. It can be assumed that the differences in the way medical devices are regulated in the two markets may have an impact on the speed tests are commercialised; the regulations for devices are more straightforward in the European market.

5. DISCUSSIONS AND CONCLUSIONS

The objective of this study was to analyse the regulatory requirements of the USA and EU at different stages of drug development process. The research questions assumed differences in the regulatory regimes of the USA and EU and that the differences might be significant in the new drug development process. In this chapter the implications between the theoretical framework of new product development and personalised medicines will be discussed, in addition to conclusions and recommendations on how the findings of this study can be used in assistance of making managerial decisions in the corporate world.

5.1. Theoretical Discussions

Three streams of literature were reviewed to gain theoretical insight in the processes taking place while commercialising personalised medicines; Innovation and New Product Development, and New Drug Development. The theories were chosen to gain further understanding on the highly structured process of drug development controlled by scientific, technological and regulatory aspects.

It was found that the description of the term innovation has evolved in the past 40 years from being considered merely as an idea or a process causing change to the widely accepted definition of a new concept needing to be successfully developed and commercialised in order to become an innovation (Abernathy & Utterback, 1978; Trott, 2005, 17). Innovation Development theories were included in this research in order to explain the concept of innovation and especially how new products are developed and commercialised.

The literature on innovation theories by different authors defined different types of innovations according to the fields of their interests, for instance Schumpeter (1964, 59) segmented innovations into being either an introduction of a new commodity or

production method, opening of a new market, changing the source of supply or reorganising an industry. In literature on technological innovation, the term was used to describe the process a new product goes through starting from the idea generation, moving through the development of the product with the help of sciences into a finalised item (Styhre 2006; Cantisani, 2005).

The study also took interest in the different models of how innovations develop from being abstract ideas into actual commercialised products. The technology push, market pull models, and the simultaneous coupling model (Chapter 2.1.2.) all identified manufacturing, marketing and R&D as the three functions that support the birth of innovation. As described in Chapter 2.1.2. the technology push and market pull models are both linear with the technology push model starting from the R&D stage, moving on to the manufacturing stage and ending in the marketing stage, whereas the market pull model begins with marketing, after which a new product is developed and manufactured. The simultaneously coupling model does not state the exact starting point of innovation but accepts the idea of the same stages taking place in the process (Trott, 2005, 22-24, Schumpeter, 1964, 58-62). In addition to how innovations come alive, the theory of how individuals adopt innovations was described. The diffusion of innovation theory by Rogers (1962, 2003) was mentioned with the attempt to understand this phenomenon.

The theories of new product development (NPD) and drug development were reviewed to gain further understanding of the stages and factors affecting the development of PMDs. Yelkur & Herbig (1996) described the stages of new product development involving generating a new idea, developing a concept based on the idea, manufacturing a product and creating a business strategy around it. Chapter 2.2 also described the various models created to describe the stages NPD involves.

The Drug Development process, though not a theory in itself, was used to provide a framework to understand about the chemical and microbiological stages of developing and commercialising drugs. Even though my research did not cover all the processes and aspects of these theories mentioned above, they helped set the stage for isolating the

post invention commercialisation of new drugs.

It was explained in chapter 2.3 that the NPD process of pharmaceuticals is divided in three stages: research/discovery stage, development stage and commercialisation stage. The research and development stages described the scientific and technologic aspects of developing a new drug, while the commercialisation stage was focused on the regulations set by the FDA and EMEA (regulatory agencies of the United States and European market areas). For the data collection of the case study, only the theory of commercialising a new pharmaceutical was relevant. The rest of the theories could not be used in the case itself but were reviewed to deepen the understanding of the process before the commercialisation phase.

Chapter 2.3.2 described the regulatory processes of commercialising new pharmaceuticals in the US market and the European market. The US market is regulated by the Food and Drug Administration (FDA) and the European market by the European Medicines Evaluation Agency (EMEA). It was found that description of the regulatory processes of drug commercialisation supports the actual impact regulatory bodies in the innovation system have in the commercialisation of new pharmaceuticals. The role the FDA and EMEA have in the innovation process is enormous. As mentioned in chapter 2.3.1 the extent of collaboration between drug sponsor and the regulator does not only limit to the review process of marketing approval but begins already before the start of clinical trials. The regulations set by the FDA follow the drug development process starting from submitting the investigational new drug (IND) application to the FDA after preclinical trials in order to get clearance to start clinical trials on humans. The regulatory agencies have been established to make sure the pharmaceuticals that are available for consumers are safe to use. However, it must be mentioned that hardly any drugs are 100 percent safe for all patients which is why in the pharmaceutical industry the term safe is used to describe a drug which benefits outweigh its possible negative side effects.

One of the key findings of the impacts the regulatory regimes the US and EU market have on the development process of personalised medicine drugs was that the Priority

Review route established by the FDA to speed up the process of commercialising new innovative drugs was used when reviewing the PMDs approved after the Priority Review initiative was established in 1992. This shows that the FDA is encouraging pharmaceutical companies to develop innovative drugs and is interested in helping the fast commercialisation of the new drugs. It was also found that the PMDs reviewed by the EMEA took considerably longer to be commercialised in the European market. It is assumed this is because of the slower process of the European agency and the differences in the market environment of the US and EU. The process on regulating the commercialisation of drugs (chapter 2.3.2.) described how the EMEA has also established a faster route of reviewing innovative drugs, the accelerated approval. However, it was found that the accelerated route was only applied to one of the ten PMDs. Consequently, the review process took much longer in the European market in comparison to the US market.

5.2. Conclusions

The desk research conducted revealed that there are vast differences in the processes and regulations the FDA and EMEA have set for pharmaceuticals and medical devices. These differences influence the speed in which new drugs are brought to the market. For personalised medicine drugs (PMDs), it seems that the drug development process is very much influenced by the same scientific, policy and market forces as for the rest of the pharmaceutical industry. However, it appears that especially in the US market, which is regulated by the FDA, PMDs are given priority review status, meaning the drugs are reviewed quicker than normally. It can be assumed that the reason for speeding up the review process is a result of a mutual understanding by the regulatory agency and drug sponsors of the importance of making new innovative drugs available for patients as soon as possible.

It was found that the development process of PMDs is likely to follow the integrated model of new product development. The model describes the NPD process as several

sequential stages, some of which may occur in parallel, and the process can be an ongoing cycle of constant development instead of being linear (Ginsburg & McCarthy, 2001). For instance, a pharmaceutical can be further improved even after it has been launched to a market by either redesigning the actual drug formula, narrowing down the patient group taking the drug to genomic sub-groups or by developing a diagnostic test to increase the medical benefits of the drug. In addition, analysis of the ten personalised medicines showed that pharmacogenomics (PGx) was applied either during the NPD process of the drugs or after the launch of the drug, in line with Webster et al's (2004) description of application of PGx in NPD process.

The application of the integrated model and PGx can be detected from how some of the drugs were developed parallel to a companion diagnostic (Herceptin, Selzentry and Erbitux), how for some of the drugs diagnostic tests were developed after the drug had been on the market for some time (Ziagen, Tarceva, Iressa, Gleevec), and how PGx information has been added to the drug's label years after its initial launch with the purpose of increasing the safety of the drug (Coumadin).

According to the analysis conducted, the number of days between submitting marketing approval application and gaining approval was less in the US than in the EU. Gaining marketing approval from the EMEA took 405 days on average for the PMDs analysed in this study, which was 95 days more than the 300 days EMEA has set as its target duration of the review process. This reveals that at least with this sample of drugs the EMEA failed to achieve its target. All of the drugs which were reviewed by the FDA were reviewed using the priority review process and on average took 166 days. The FDA has set 180 days as its target to review drugs with priority status which was clearly achieved with these PMDs. In conclusion, the review process took the European agency 239 days longer than the US agency.

The EMEA reviewed two drugs under a special status; Selzentry on the accelerated route, and Gleevec as an orphan drug. It could be detected that for both of the drugs the review took less than 300 days (285 and 255), which was considerably less than the average of 405 days. Thus, it seems the accelerated route or orphan status actually

accelerates the process as it is supposed to even though the normal route of approval takes longer than the European agency's target.

The time lapse between gaining marketing approval and launching a new pharmaceutical was also shorter in the US than in Europe. Therefore, it could be concluded that the whole process of commercialising a new pharmaceutical product happens faster in the US than in Europe.

The reason behind the difference in the time lapse of commercialising (time from submitting marketing approval until launching a new product) new pharmaceuticals in these two markets could be described multilayered. Obviously, the way how the regulating agencies handle the marketing authorisation process has the most remarkable influence in the speed of commercialising new pharmaceuticals. Their processes are again influenced by the overall market environment they operate in and the issues on the agenda of the policy makers in that specific market area. As market environments, the US and EU are very different. For instance, the EU market is bigger in size and more heterogeneous. Since the European Union consists of different countries, it can be assumed that the level of bureaucracy is higher when the legislation and regulations of individual countries have to be taken into account as well. Not to mention how the EMEA marketing authorisation process involves more parties (the EMEA, national authorities, European Commission)in comparison to the more centralised structure of the FDA.

It was found that the time lapse between a drug and its biomarker test being launched was shorter in the European market than in the US. It can be assumed that the reason behind this is closely related to the emphasis the regulatory agencies of the two market areas have placed on biomarker testing. Diagnostic tests for six of the ten drugs were declared mandatory by the EMEA, whereas biomarker tests for only three of the drugs were set mandatory by the FDA. This discrepancy is probably also a result of how marketing diagnostic devices is regulated in the two markets, which again is connected to the level of significance the two regulators have set for combining diagnostics with therapeutics.

Another factor which may have an impact in the speed in which newly developed PMDs are pushed to the market is the rareness of the disease or medical condition the drug is designed to treat. For instance, the orphan drug Gleevec was commercialised within a day after gaining marketing approval in the US market (orphan drugs are designed to treat diseases or medical conditions affecting only 5 individuals in 10000). However, further research on this aspect would be required since Gleevec was the only orphan drug included in this case study. In addition, it would be interesting to know whether the drugs that fill an unmet need in the market, such as Gleevec, are commercialised faster in comparison to drugs that have been developed to treat patients in illnesses and/or medical conditions for which some sort of therapy already exists.

5.3 Managerial Implications

From a managerial point of view, the findings of this thesis can give ideas on which market should a pharmaceutical and/or diagnostics company launch their new product in first. Since developing new pharmaceuticals and medical devices is an extremely time-consuming process that costs millions of dollars or euros, it is expected that the companies want the new products out in the market as soon as possible in order to start gaining revenue. To achieve this, and to avoid unnecessary costly delays, managers have to be very familiar with the policies of the regulatory agencies.

As mentioned, the overall process of commercialising new PMDs was faster in the United States than in Europe. In the US, on average the number of days between drug sponsor submitting marketing approval application and launching a new product was 179 days. The comparable figure for EU was 432 days. Also, for most of the PMDs the faster review route designed for highly innovative drugs was used in the US but not in Europe. On one hand, this could give an insight of aiming to launch a new PMD first in the US market in order to start making sales while waiting for the EU marketing approval and creating marketing strategies for the European countries the drug sponsor wants to launch the new PMD in. On the other hand, since discovering and developing a

new drug might take ten years, one might wonder whether this difference of merely eight and half months is significant.

It must be mentioned that whilst making decisions on which market should one launch their product in first, there are issues such as policies of healthcare authorities and reimbursement of cost of drugs that a manager should look into in addition to the regimes of the FDA and EMEA. Since pharmaceuticals for serious diseases are usually extremely expensive, welfare countries establish policies on how much of the state's budget allocated to healthcare can be used to pay part of the costs related to treating its citizens. Nevertheless, the whole aspect of reimbursing pharmaceuticals is such a wide topic that another research would have to be conducted in order to look into that aspect in the managerial decision-making of choosing the first launch country for a new product.

It was found that the time lapse between gaining marketing authorisation and launching a new PMD was on average 14 days quicker in the US than in the EU. What may cause the delay for companies of launching new pharmaceuticals in the European market is the size of the distribution channel that expands over country borders, whereas in the United States the distribution channel is most likely more homogeneous with fewer parties involved in the process. It can be assumed that the size of the market and number of actors involved in the commercialisation process of a new product has a direct impact in the time the procedure takes.

The aspects mentioned above taken into consideration, it is recommended that managers should make the decision on which market to commercialise a new pharmaceutical in first, based on the level of innovativeness the regulator places on that particular drug type. This recommendation is reasoned with the finding that for the PMDs analysed in this research, the FDA reviewed most of them with the faster review process which is specially designed for highly innovative drugs but the EMEA used the standard review. Thus, it seems that the US regulatory regime is more favourable towards highly innovative drugs than the European regime, making the US market the better option to commercialise a new drug in first.

It is also recommended that managers of pharmaceutical companies should concentrate on keeping the communication flow between the company and the regulatory bodies ongoing through the whole development process of new drugs. If the level of communication is high throughout the process, it is more likely that the marketing approval review happens faster and consequently the pharmaceuticals can be launched in the chosen market quicker.

Whereas launching a new PMD was faster in the US, the time lapse between a drug and its biomarker test being launched was shorter in the European market. In addition, six out of the ten drugs analysed had biomarker tests that EMEA had declared mandatory to use in combination to the therapeutics, in comparison to the FDA only demanding three of the drugs to be accompanied with the tests. Thus, this finding shows that the European market is more favourable market area for diagnostics companies who operate in the field of personalised medicine.

The status the regulatory agencies set for diagnostic devices is significant in their commercial success. It can be presumed that if conducting biomarker testing before starting medicinal therapy is mandatory, the adoption rate of physicians prescribing testing is higher. Consequently more tests are being sold. Hence, it can be concluded that such a regulatory environment that encourages the usage of biomarker testing would be more appealing to diagnostic companies.

Knowing that there are differences in the regulatory regimes of the US and European market and that these differences impact the commercialisation process of new PMDs can help managers to improve their own performance and consequently the company's performance. Having the knowledge of the scientific and technological aspects taking place during new drug development and understanding the complexities of the market has a direct influence in managers' capabilities in making informed decisions. At the end of the day, the pharmaceutical industry exists to improve and maintain the well-being of humans and it seems that the personalised medicine approach is especially emphasising the application of state-of-the-art technologies to improve the quality of healthcare.

5.4 Implications for Future Research

It was learned that the process of developing new personalised medicines is influenced by the same scientific, policy and market forces that shape drug development in other areas of the pharmaceutical industry. However, it seems that the regulatory policies and pharmaceutical industry in general is trying to encourage the application of personalised medicine in new drug development.

The topic of this research was extremely wide and was narrowed down with the research questions set in the beginning of the research process. The research conducted could have been much further expanded with using a bigger sample of drugs or using completely different research methods, for instance adding the aspect of primary research by interviewing drug sponsors or regulatory bodies.

If this research was continued, I would like to add the element of reimbursement to the commercialisation process. As mentioned, whether a drug is being reimbursed in the target market can have a significant impact in its commercial success. Thus, it would be extremely useful to look more deeply into that aspect in addition to the regulatory regimes impacting the process.

In addition, it would be interesting to know whether the make of the drug, in terms of whether the drug is a biological drug or a small-molecule drug (SMD), has an impact in the timeline of its commercialisation. However, for this to be discovered, the sample group would need to have an equal amount of biological drugs and SMDs.

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APPENDIX 1

Appendix 1 Drugs and Tests in Both Markets According to Biomarker

Drug	Valid Genomic Biomarker	Diagnostic Test available in the US	Diagnostic Test available in the EU
Herceptin	HER2 +	HercepTest	HercepTest
Erbitux	EGFR +	Dakocytomation EGFR pharmDx test kit	Dakocytomation EGFR pharmDx test kit
	KRAS	KRAS LDTs	DxS TheraScreen KRAS
Selzentry/ Celsentri	CCR5 Chemocine C-C motif receptor	Monogram Trofile	Monogram Trofile
Vectibix	EGFR +	Dakocytomation EGFR pharmDx test kit	Dakocytomation EGFR pharmDx test kit
	KRAS	KRAS LDTs	DxS TheraScreen KRAS
Iressa	EGFR-TK	Genzyme EGFR	DxS TheraScreen EGFR
Ziagen	HLA-B *5701	Labcorp HLA B5701	Delphic HLA B5701
Tarceva	EGFR -	Genzyme EGFR	DxS TheraScreen EGFR
Tamoxifen	CYP2D6 variants	Roche Amplichip	Roche Amplichip
Coumadin	CYP2C9 Variants, VKORC1 Variants	PGx Predict Warfarin	n/a
Gleevec/Glivec	C-Kit	DakoCytomation C-Kit PharmDx	DakoCytomation C-Kit PharmD