Commercialization Strategy for the Pharmaceutical Industry

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by

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Foreword & Acknowledgements

According to a report by the World Health Organization in 2009, there were about 34 million counterfeit and substandard medical pills/tablets in distribution across Europe, which had been seized by the European Union in a mere period of two months. While a common human tendency attributes such potential hazards to administrative malfunctioning, a deeper scrutiny revealed that the major reasons behind it were exorbitant manufacturing costs of the original tablets, the ever increasing need to create a competitive advantage, fragile supply chains, and poor-quality management measures. Observing these implications in the very industry that my father earns his bread and butter with, I became aware of the exigent need to optimize. Over the years, I have seen him address production, quality, and cost issues simultaneously while contriving strategies for future growth in his small-scale pharmaceutical unit. I realized that a combination of technical finesse and business acumen is quintessential to an industry's growth.

A lot has changed ever since, in the technological, economic, social as well as the regulatory regimes in which the Pharmaceutical Industry operates. Having close association to it while I grew up, I realized that this is an industry which has a tremendous impact directly on the well-being of people. I became fascinated to find out more on how the industry is developing and more so often what factors are driving its growth and what are detriments to it. So, I chose to delve deeper into this topic as my graduate thesis. My motivation to do so was amplified by the fact that striving to somehow find common ground between the health/medical needs of the people and their facilitators (pharma companies, healthcare organizations, regulators, doctors etc.) could completely revolutionize society as a whole; alleviating the suffering of the human kind. While I concede that finding common ground between various entities to achieve the grandeur of a world with lesser suffering - is a far more complex topic and largely beyond the scope of my research, I surely think that comprehending the position of one of them (the Pharmaceutical companies as a whole) will bring us a step closer to it.

With this, I would like to convey my sincere gratitude to my mentors Dr Roland J Ortt and Dr Mark De Bruijne - without whom this research wouldn't have been possible. They played a crucial role in helping me to pinpoint my research scope after having multiple rounds of discussion with me. Additionally, I would like to take a moment to appreciate the openness and directness of both my mentors. Be it my research project planning, setting up interview protocols or interpreting results, their critical evaluation of my work has pushed me to improve at each stage of my research. I would also like to thank the experts who agreed to share key insights with me. Lastly, I'd like to thank my friends and family for their support throughout.

Abstract

This thesis report is aimed at analysing two phenomena, the first being - the major trends which are shaping the pharmaceutical industry currently. The industry is witnessing massive strategic shifts, routine upgrades to new drug technologies in a dynamic regulatory and market environment. The growth rate of the global pharmaceutical industry is projected to exceed 1 trillion dollars by 2022 (Lervolino & Urquhart, 2017). There are increasing expectations from pharmaceutical companies to introduce advanced products and technologies for the welfare of the people. This objective of this descriptive study is to analyse market, technological and strategic trends, the interrelations, and to some extent, the impact of regulatory environment on the pharmaceutical ecosystem. Secondly, this study lays a special emphasis on personalized medicine and assessing its current and future scope amid these changing dynamics. A combination of systematic literature review and expert interviews was undertaken to achieve the above stated objective. The study is qualitative and involves analysis of opinions derived from expert interviews cross verified with scientific literature. The key findings are stated below:

Since traditional pharmaceutical companies now face increasing market and regulatory pressures to differentiate their products, they are looking for alternate business models. This pressure is supplemented by a change in payer preferences and healthcare budgets set by governments across the world. High risk of drug failures further adds on to this. Many companies are experimenting with radically different product lines such as biologics and biosimilars. In the recent years, pharmaceutical companies in conjunction with biotechnology companies have identified the potential of technologies such as genetic profiling, advanced diagnostics etc. to understand the effects of drug interactions with the human body. However, the use of such technologies remains largely confined to highly specialized therapeutic areas such as oncology. The main reason is the economic barrier it faces. The costs of most personalized drugs are extremely high, and this affects the market access of a drug. It was also found that, the readiness of the facilitating environment (patient data repositories, Information technology infrastructure) etc. is also essential for commercializing personalized medicine. Healthcare Institutions, service providers are still not equipped to deal with personalized medicine on a mass level. Hence personalized medicine is predicted to remain as a niche offering limited to a select few therapeutic areas such as oncology in the foreseeable future.

Two promising avenues for rapidly commercializing personalized medicine were identified: The first relates to develop financing mechanisms for pharmaceutical companies so that they can develop novel drugs for people with serious medical conditions. The second avenue which was identified was designing optimal risk sharing agreements between pharmaceutical companies and the payers.

For a detailed understanding of all trends, the relationships amongst them and the industry readiness to transition to personalized medicine, please refer to this report.

Keywords: **Pharmaceutical, personalized medicine, drug, trends, interrelations, strategy**

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1. Introduction

This chapter provides a basic understanding of the pharmaceutical industry and the relevant stakeholders. Next, the knowledge gap and the research objective are explained. To fulfil the stated research objective, a 'main research question' is formulated. That main research question is then fragmented into three sub-research questions to help understand each associated concept clearly. The chapter ends with a clear definition of the scope of this study.

Overview

The pharmaceutical industry has long been associated with solely the research, development and manufacturing of drug complexes. Until now, the industry role was that of an almost independent actor only fulfilling its scientific targets (in terms of discovery of new drug molecules) and legal compliances (meeting the guidelines by various regulatory authorities in terms of safety and performance of therapeutic drugs). However, there have been significant disruptions in the recent years which have completely altered this position of the industry. One of these disruptions is the near obsoletion of the all in one blockbuster business model – which was focused on developing only those drugs which could give at least $I billion annual revenues via sales. On the other hand, a steady rise of the business models targeting niche customers(PricewaterhouseCoopers, 2009).

Other changes that demand a change in the operational models of the pharmaceutical industry are patent cliffs (expiration of blockbuster drug patents) which have enabled many small-sized generic drugs producing companies to compete head on with pharmaceutical giants by inundating the market with cost effective versions of expensive blockbuster drugs. This research is based on this ever-increasing need for big pharmaceutical companies to strategize to either differentiate, diversify, network or collaborate in order to expedite their product development pathway to being market ready. This is done to not only retain and expand their market access but to also improve quality of treatment options available to the end users.

Secondly, with the advent of various independently run diagnostic and biotech companies getting success in human genetic profiling and studying drug responses, a new concept of Personalized medicine has emerged. Furthermore, the race to achieve a competitive advantage has led the pharmaceutical-healthcare conglomerate globally to look forward to offering tailor made solutions to its users. This has also been substantially influenced by the demands and needs of relevant stakeholders (patients, payers, retailers, regulatory authorities) etc. Since the market success of a pharmaceutical company depends upon the reception of their products/services by these stakeholders, it becomes vital for the pharmaceutical industry to adapt to the changing environment.

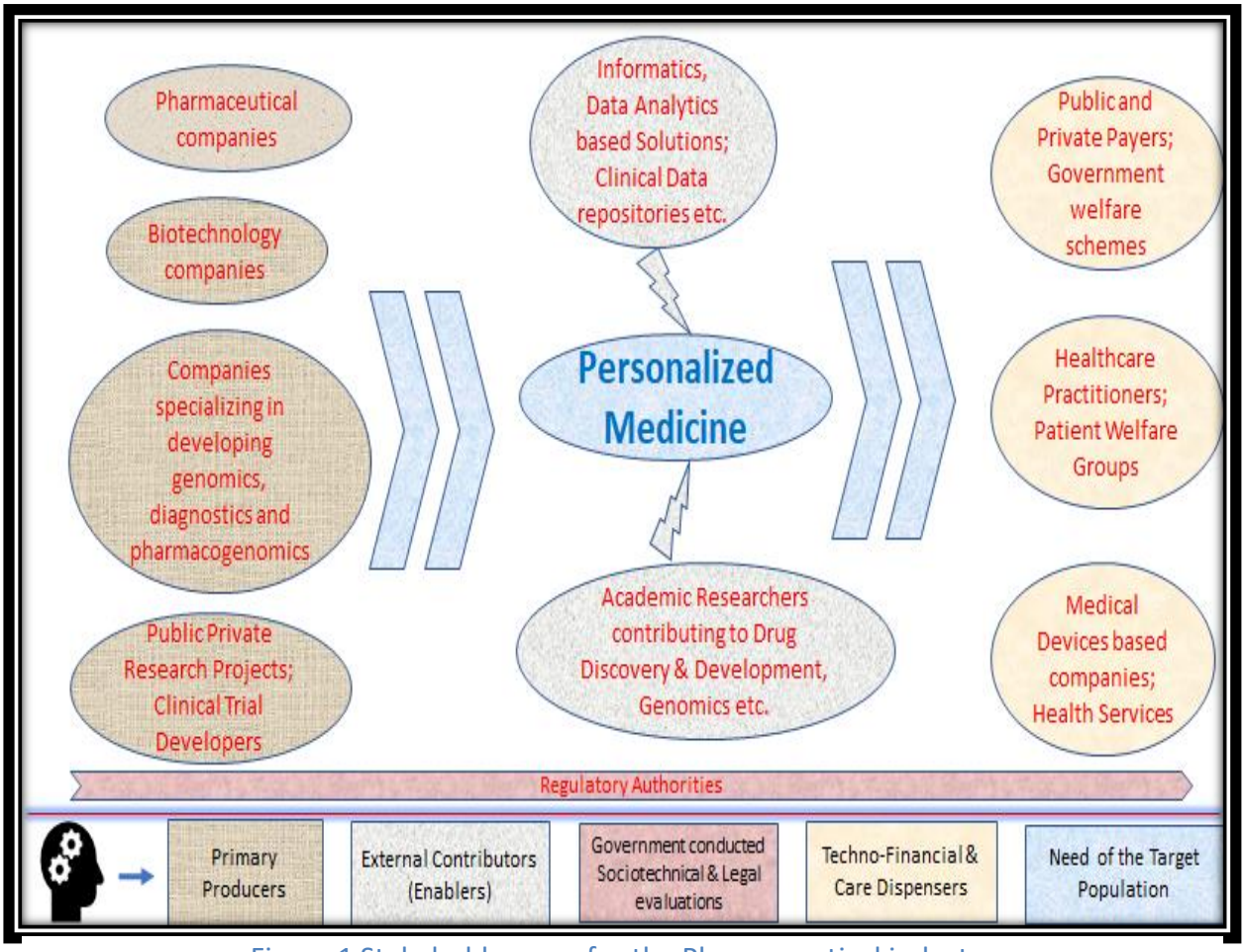

Figure 1 Stakeholder map for the Pharmaceutical industry

Figure 1 represents a simplified representation of the stakeholders involved in the pharmaceutical industry. This figure is showcased as an attempt to understand the role of each stakeholder and their importance phase wise during a new personalized medicine-based project. The primary producers are the players who survey market needs and start developing as well as commercializing new drugs, or combinations of tests and drugs. The enablers are those stakeholders which expedite the process of development undertaken by the primary producers. They expedite the process by identifying potential drug targets that can be taken up by the pharmaceutical industry. Often, the enablers act as a decision support system for the primary producers. Once, the product is ready, the 'Techno-Financial & care dispensers' take the product to the target population. They include payers (insurance agencies or government schemes) who provide finance to the target. The dispensers also include the 'tech' providers - tech which often goes in combination with the product. For example, medical devices which administer a drug. The dispensers also include healthcare professionals, doctors etc. who are the most important part of the dispensing stakeholders. Put simplistically, the output from the primary producers is as an input for the dispensers. Throughout this process, the primary producers, enablers and the dispensers operate in sync with the regulatory authorities.

However, it must be acknowledged that, the process of developing and successfully commercializing Personalized Medicine is not always completely linear (as it is shown in the figure). The primary producers and the enablers often work hand in hand right from the very beginning to determine which project options are viable for development and which

options to exclude. Similarly, more and more post-market research (after dispensing) often steers the future course of new drug development for the primary producers. These iterative interactions are not shown in the figure for the sake of simplicity.

Scientific Knowledge Gap

At present, there lies a gap between the alignment of interests between the developers of new molecular/genomic diagnostics with that of traditional drug manufacturing pharmaceutical companies. Also, pharmaceutical companies often are unable to stabilize between investing resources to develop new therapeutics in the conventional manner or to merge personalized medicine which is still in its incipient stage (Jakka & Rossbach, 2013). Many pharmaceutical companies find themselves in a disarray in order to handle growing payer influences in shaping market requirements (and thus the direction of drug/therapeutic service development). Some have responded by trying to perform small scale regional collaborations to comprehend payer needs to little success, but a structured strategic response is largely missing. (McClearn & Croisier, 2013). Although, there is some literature on the trends affecting the pharmaceutical industry, no attempts have been made to see the interrelations amongst the different trends. Personalized Medicine as a concept is extremely new and has been accruing significant scientific interest only recently. While there are some scientific studies that attempt to assess the probable barriers, or economic or technological potential of personalized medicine, they often lack a multi-stakeholder perspective to problem solving. This cohesive study attempts to bring all these lacunae together and create a meaningful understanding of how pharmaceutical companies should approach their business model.

Research Objective

The research objective provides us with the end goal of what we want to accomplish as a result of conducting this study. The objective of this research is as stated below:

To identify techno-commercial trends and interrelations affecting the pharmaceutical industry and determine the industry readiness to switch towards a Personalized Medicine based Strategy.

To gain knowledge about any industry, it is vital to consider the setting in which that particular industry operates. Since, the pharmaceutical industry functions in correspondence with the regulatory authorities right from product development to shelf, the impact of regulatory guidelines on the industry's functioning is crucial to understand any strategic implications or new business models. Hence, even though assessing regulatory challenges isn't the primary goal of this study, direct regulatory impacts on upcoming pharmaceutical research or products will be considered. Based on the trends and the interrelations amongst them, hindrances, needs and opportunities to change the strategic focus will be assessed. This assessment will be focused on determining the commercial viability of a possibly revolutionary 'Personalized medicine Strategy'. The outcome of this research will provide a clear strategic direction to Big Pharmaceutical companies which currently are faced with innovation dilemmas, diminishing new product developments as well as disruptions to the dominant standard set by their own previous business model.

Research Questions

The main research question for the thesis proposal is as stated:

To what extent does a Personalized Medicine Strategy fit in with the new trends and disruptions in the Pharmaceutical Industry?

The sub research questions are framed in such a way that the collective insights obtained by answering each sub-research question will help us to effectively answer the main research question. The sub research questions are as follows:

1. What are the current trends observed in the Pharmaceutical industry?
2. What are the interrelations observed between these trends?
3. What is a Personalized Medicine Strategy? How can Personalized Medicine be commercialized?

A brief answer to the following question will be included in the post research Discussion since the topic is relevant but not the main focus of the research:

What are the risk sharing mechanisms that can be used by the Pharmaceutical Industry to propel the adoption of Personalized Medicine?

Societal Relevance

The societal relevance of this research can be seen in the form of a drastic increase in the number of end consumers receiving adaptive treatments offered in sync with routine conventional drug treatments. Analyzing barriers and opportunities due to disruptions will bring out unmet patient needs in the future. Since, the end goal is also to improve health outcomes and not solely increase revenues for the pharmaceutical industry, it is very likely that packages offering optimal combinations of drugs, medical devices, preventive care, monitoring plans etc. would gain precedence over conventional treatments in the long term. Strategies intended to enable a transition to improve health outcomes are thus likely to create a positive network externality. It means that as the installed base increases, it is likely to lead into a self-reinforcing cycle of value creation for the pharmaceutical industry (Schilling, 2013).

Scope

The scope of this proposal is limited to explicate possible strategic options that Pharmaceutical companies could undertake in order to:

- Transition to a more robust business model with lesser uncertainties and product failures (via risk sharing) than the traditional blockbuster model
- Commercialize at a mass level - Personalized Medicine and in turn help establish Customized treatment solutions (which are directly correlated to changing market expectations and preferences)
- The region of analysis has been restricted to the United States of America and Europe only. The rationale behind doing so is the fact that most of the big pharma companies operate in both the locations. Furthermore, the technological advancements in Europe and United States is comparable and often interdependent

on each other. The thesis doesn't aim to finetune on the implementation. Implementation would require the knowledge of operations of not only the manufacturing firms but also of associated organizations such as Regulatory agencies, payers etc. which is beyond the scope of this thesis.

2. Research Design, Methodologies and Protocol

In this chapter, the research design framework is discussed. The constituent elements of this research design will be explained. Subsequently, the appropriate research methodology fitting the research design is discussed and its selection is justified. The methods of data collection and analysis are mentioned, just after. Finally, towards the end of the chapter, the division of research tasks is clearly explicated.

Research Design

(Sekaran & Bougie, 2016) define research design as "a blueprint or plan for the collection, measurement, and analysis of data, created to answer your research questions." Based on the theoretical research framework developed by (Sekaran & Bougie, 2016), the constituents of this particular research design are mentioned below:

- Study Type: As a social scientist investigating the dynamics of the pharmaceutical industry, the first decision that needs to be made is regarding the type of study that needs to be conducted. Broadly, the study types can be categorized as quantitative qualitative, or mixed methods-based studies (which involve a combination of quantitative and qualitative studies). A quantitative study is the preferred study type when clearly defined variables are used to assess the impact on other unmeasured parameters. When numeric answers or probabilistic estimates based on inputs of data is needed, quantitative studies are usually the preferred type. A qualitative study type is chosen in order to comprehend a phenomena through various perspectives or individual standpoints (Hammarberg, Kirkman, & De Lacey, 2016). A mixed methods-based study type is usually undertaken when it becomes difficult to achieve the research objective with standalone qualitative studies or qualitative studies (Sekaran & Bougie, 2016) In this study, we choose a qualitative study type since the objective is to determine variables (in this research : trends) that affect the subject of investigation (in this research: pharmaceutical industry). Based on those preliminary findings, interrelationships between trends will be identified. One could argue that such interrelationships can be obtained quantitatively as well as qualitatively. But since, any analysis on the subject – the pharmaceutical industry inherently contains multiple actors and stakeholders, based on the research framework developed by (Hammarberg et al., 2016), we choose the qualitative study type. This is because a qualitative study would enable us to retain the intricacies of the subjective viewpoints presented by multiple stakeholders as opposed to being categorized as numeric data points in case of a quantitative study.
- Research Strategy: A combination of systematic literature review with a survey-based research is chosen for this study. The systematic literature review would help in building a preliminary understanding of the pharmaceutical industry, the problems already identified in scientific literature. The 'survey' will contribute to this study by (i) validating literature findings (ii) giving additional undiscovered insights on trends and interrelations as well as the current developments in personalized medicine

(iii)revealing stakeholder perspectives and perceptions (iv) helping us to identify key points for the qualitative analysis

- Study Setting: As per (Sekaran & Bougie, 2016) the study will be conducted in a 'non contrived ' setting which means that the phenomena will be observed under its existing natural conditions.

- Study Characteristics: Based on the research designs explained in (Sekaran & Bougie, 2016), this study is 'descriptive' in nature. The reason why a descriptive study is preferred is because it does not necessitate the researcher to adhere to a pre-developed conceptual framework. Secondly, descriptive research allows sampling flexibility which can be utilized by the researcher to evoke rich data. The characteristic attributed with this study are 'correlational'. There is a fine difference between causal and correlational studies. While, correlations amongst trends will be analysed as a part of this study, they must not be confused with causality. In order to find causality, the study setting must be manipulated – which then allows us to observe the effect of varying independent variables on dependent variables. But, in this study, we observe the functioning of the pharmaceutical industry without manipulating any variables and thus the study is correlational.

- Time Frame of the Study: The study conducted is a 'one shot study' since data is gathered and analysed over one continuous period of 6 months.

- The Unit of Analysis: In this study, the unit of analysis is the pharmaceutical industry Any recommendations that are given as a result of the analysis will be made by considering the entire industry whole and not specific to one company.

Data Collection Methods

The primary data collection method chosen for this study is in depth semi-structured interviews – a type of survey-based research. Semi structured interviews allow room to focus on previously unanticipated, yet, important issues raised by an interviewee. Quoting (Hammarberg et al., 2016), " Qualitative research techniques include 'small-group discussions' for investigating beliefs, attitudes and concepts of normative behaviour; 'semi-structured interviews', to seek views on a focused topic or, with key informants, for background information or an institutional perspective; However, for this study, rather than conducting group discussions, the interviews were conducted one on one since the interviewees were from different locations with differing schedules. The secondary data collection method was a desk based systematic literature review. All key insights obtained from desk based systematic literature reviews are corroborated with the experts.

The reason why focus is given on conducting interviews (from a diverse set of professionals) is due to the peculiar nature of the pharmaceutical industry. Any limitations in the drug development pipeline (initial part of the value chain) are directly reflected in the resource allocation (end part of the value chain) for the commercialization departments. Pharmaceutical companies often struggle with innovation dilemmas across their value chain (Seiter, 2005). For example: Should pharmaceutical companies try and optimize existing

profits or should explore new business avenues at the cost of current profits? Each strategic decision has a different implication across different parts of the value chain. For example, to explore a new business opportunity, let's say the introduction of a new drug product - the pharmaceutical company might choose to increase its R&D expenditure and simultaneously curb excessive spending on sales and promotion of its existing products. To understand the net effect of such a strategic decision, it is important to involve all major stakeholders for the value chain. It may be possible that a decision which is very positive for one stakeholder, might be a detriment for the other. By transforming subjective views of involved parties into priorities and preferences, hidden correlations and points of divergence between different stakeholders can be identified (Valenta & Wigger, 1997).

As for the secondary data, a desk-based systematic literature review was done. Figure 2

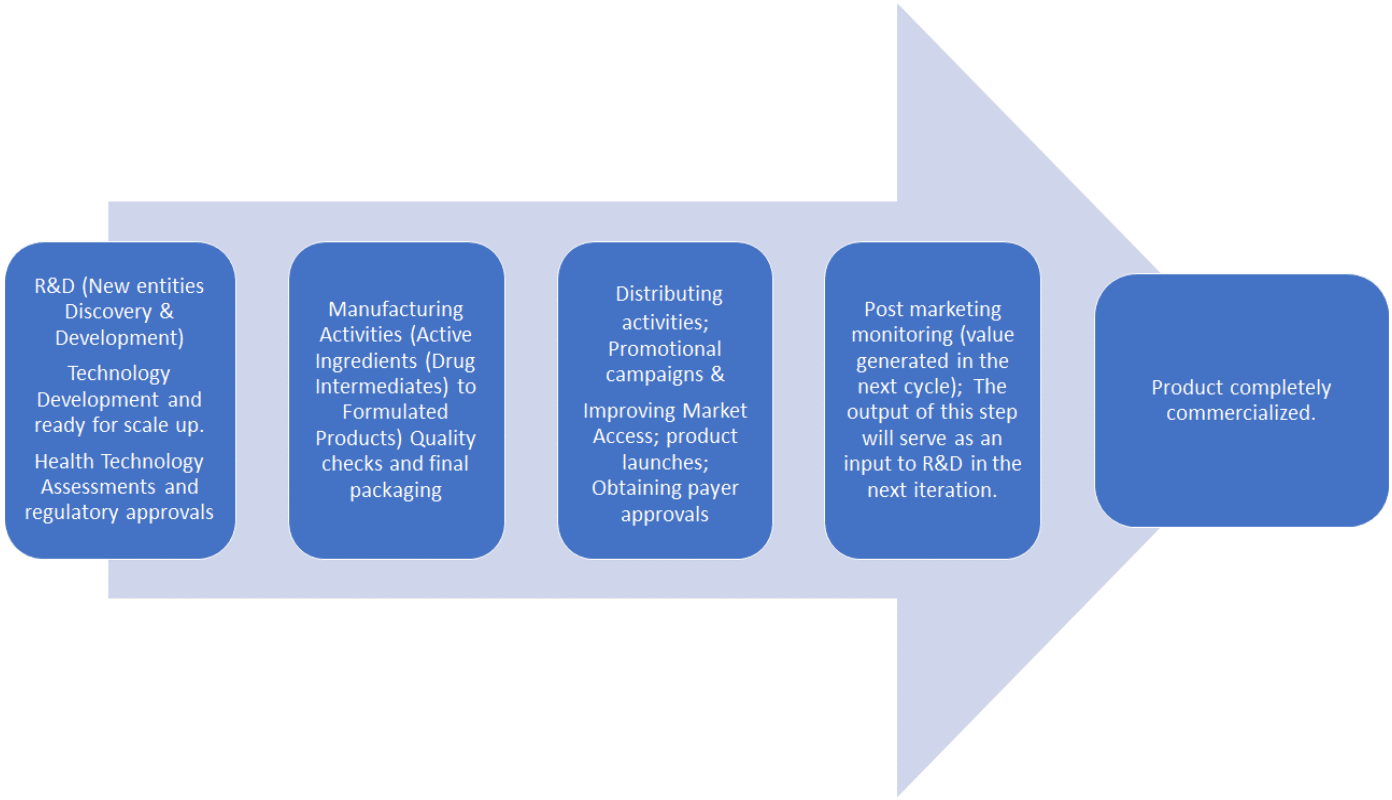

Figure 2 A schematic representation of the pharmaceutical value chain

depicts the different phases of research. The logic of the literature review is as follows:

The search began with a preliminary list of keywords and phrases. 'Pharmaceutical' 'trends', 'Blockbuster drugs' 'Business Models in the Pharmaceutical Industry', 'Commercialization in the Pharmaceutical Industry', were used to begin the search. This was done to get a sense of the possible problems faced by the industry. More than 300 scientific articles, reports and documents were found and briefly skimmed through as a result of the preliminary search. Only those scientific articles/papers/reports which focused on the Pharmaceutical Industry in Europe and USA were considered for review since the research scope was set accordingly. The logic behind limiting these articles/reports was based on the fact that: There are significant differences in regulations and technology levels between EU/USA and developing

countries in Southeast Asia or Africa. Comparing EU/USA with Asia/Africa or other developing countries, there are:

- Extreme differences in average income levels – which affects affordability of a new innovation/technology/product
- Varying degrees of supporting pharmaceutical infrastructure
- massive differences in appetite for absorbing expensive new technologies
- regulatory differences

Hence, if the potential of a new technology or concept is to be evaluated, it would make more sense if that potential is evaluated separately for two different markets rather than considering them as similar.

Six main databases were searched with the aforementioned keywords/phrases to get a high-quality peer reviewed scientific, academic and corporate research. The databases used for this search were: 1) National Center for Biotechnology Information (NCBI) which is a subsidiary of the National Institutes of Health (USA). 2) Springer Nature 3) Science Direct 4) Scopus – an Elsevier owned database 5) Google Scholar 6) Research Gate. Several masters and doctoral thesis in the field of pharmaceutics, Medicine, Financial modeling were also used supplementary to the five main databases.

For information on the regulations in the pharmaceutical industry, two primary sources of information were considered: Publications, Regulation guides, or dossiers by: 1) The EMA which stands for the European Medicines Agency and 2) USFDA (United States Food & Drug Administration) The detailed list can be found in the 'References section'.

After the preliminary search ended, the problem area and knowledge gap were clearly identified. Based on that, the next phase of literature search (phase II) included seven important key phrases that were not a part of the preliminary phase. 1) 'Personalized Medicine strategies' 2) 'Risk Sharing' 3) 'Payers' 4) 'Interrelations among trends in the pharmaceutical industry' 5) Risk Sharing in the Pharmaceutical Industry

At the end, a total of 108 documents (scientific reports/articles etc.) are considered for the final literature review. It should be noted that although the systematic literature review was concluded in phase 2 of the research (as per Figure 3 on the next page) – The findings from phase 4 of the research were compared with phase 2 findings. For clarification of some complex concepts, additional documents have been referred as and when needed during phase 4 of the research. Refer to Figure 3 for a clear understanding of the research flow.

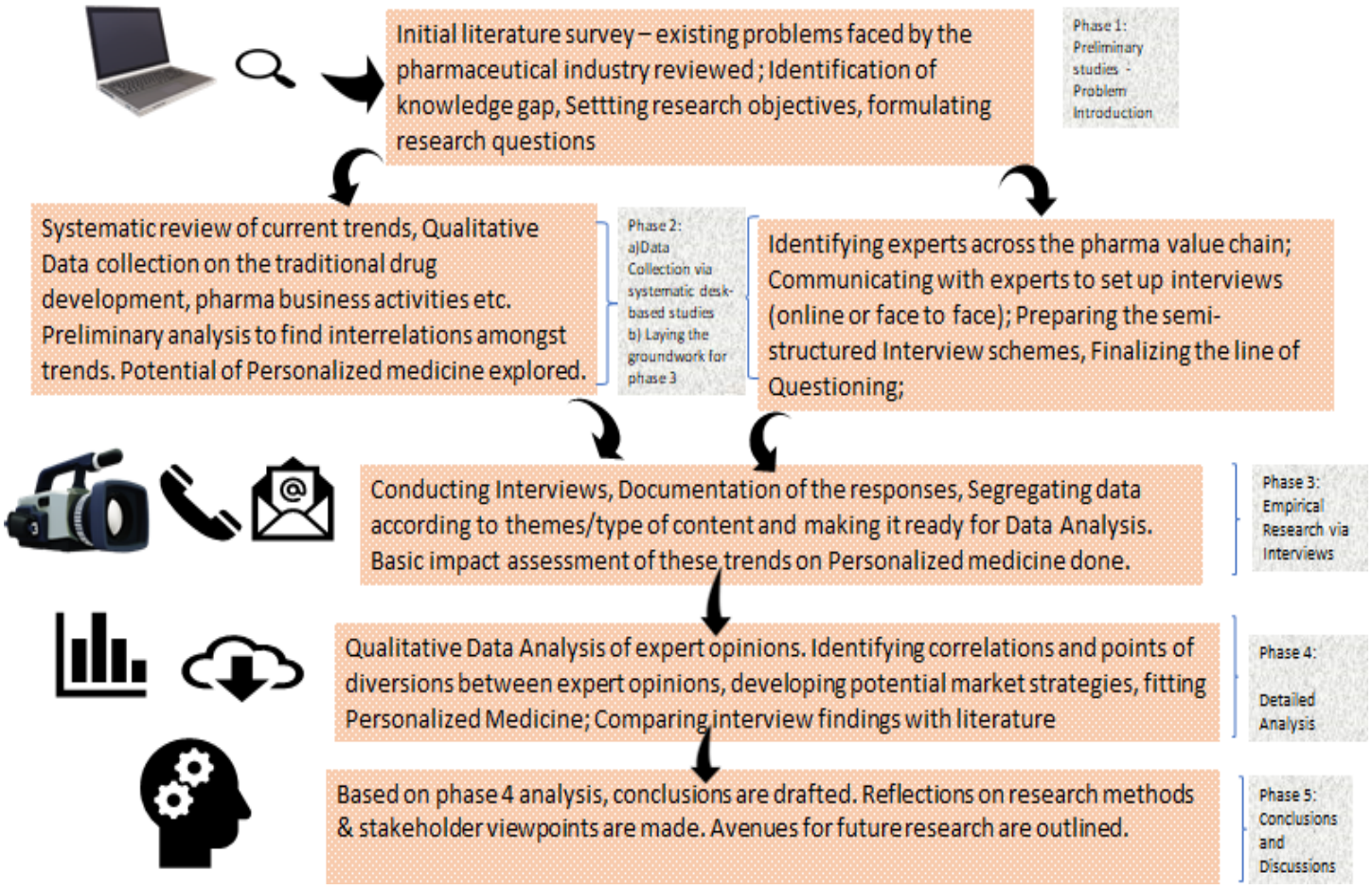

Figure 3 Research Flow Diagram

It must be ensured that the secondary sources of data collection are well recognized by the scientific community either through peer reviews, publications in high impact factor journals etc. A significant part of this research depends on industry experts as a primary data source as well as for validation of the secondary data. Hence, the establishment of 'research credibility' is crucial. This can be done by setting a variety of parameters for expert selection. The interviews will be either conducted face to face or be done via the web through skype or telephonically. The transcripts of the interviews will be recorded verbatim. Use of a real time smart transcription tool 'Otter' will be done to handle large transcripts/texts and audios. After each transcript, Otter's software will auto-generate a list of most frequently used key-words during the interview. Also, data can be segregated under software created themes if needed. The rationale for the interviewee selection criteria was as follows:

(i) The experts should head executive or scientific departments in pharmaceutical/biotech companies operating in Europe/USA or be the director level.

(ii) The experts having a minimum work experience of 10 years in the Pharma/Healthcare/Biotech sectors are selectively chosen with one exception. The rationale behind assigning an arbitrary value of 10 years is based on the assumption that 10 years is a substantially long period to witness the transformation of the industry, current challenges and opportunities of growth. If the industry work experience demonstrated by the selected expert is less than 10 years, then the selection criteria for the experts is that they should hold at least a PhD or an industry equivalent of a PhD in their field of work.

The selection of experts is done by dividing them into 4 different but interconnected fields of expertise across the pharmaceutical value chain.

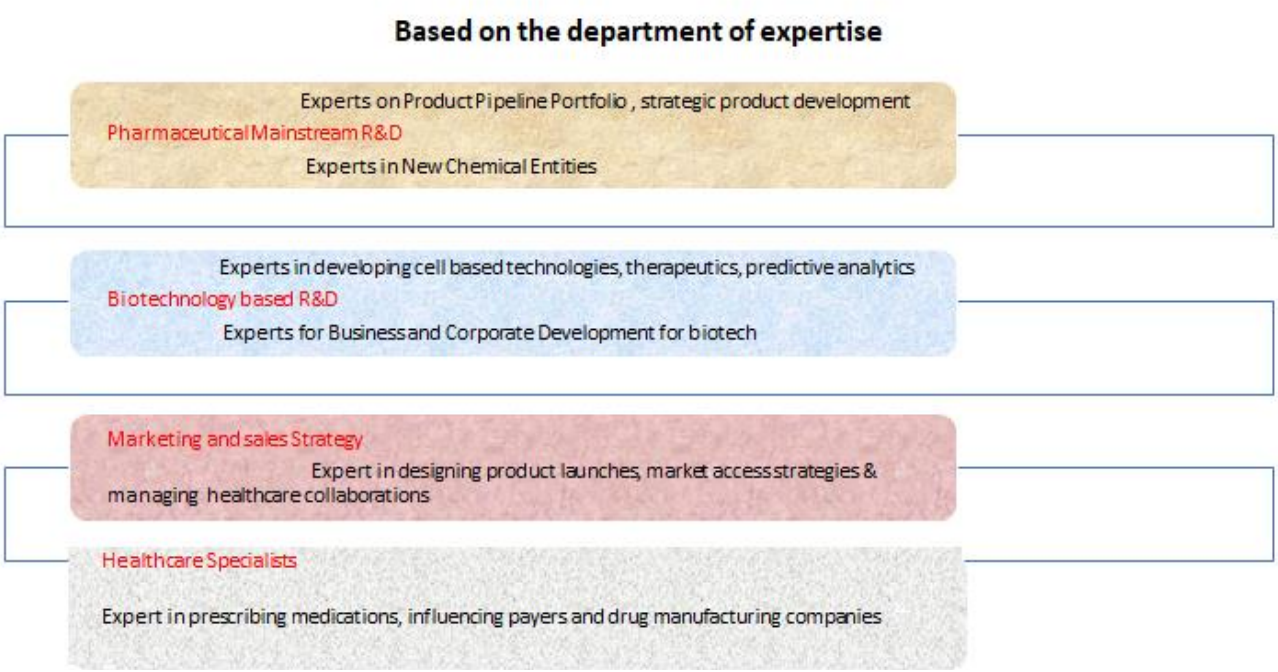

Figure 4 Expert Selection Process

Interview Protocol

5 Semi structured interviews with professionals from major Pharmaceutical Industries will be carried out. Each respondent was sent a research outline prior to the interview. The research outline contained the objective of the thesis, an introduction to the topic and a list of interest areas which were mapped with the respondent's expertise. Each interview was designed in a way that the initial questions were open-ended broad questions and then gradually, they were narrowed down as per the respondent's answers. The open-ended questions were asked to get an unbiased first opinion from the experts. Other than some sub-conscious biases that creep in during the process of interviewing, the open-ended questions were prepared in a very neutral frame to keep interview bias as low as possible. The course of data collection was stopped as and when 'informational redundancy' occurred (Sandelowski, 2008 as cited in Saunders et al., 2018). The list of questions can be found in the appendix of this thesis. For selecting the interviewees, a variety of stakeholders in the pharmaceutical value chain were considered and the following have been chosen. The names of the stakeholders have been anonymized for confidentiality reasons.

Interview 1 was conducted with (Expert 1) the President of a Pharmaceutical company which has a major focus on research as well as manufacturing and formulation of drugs in the European and American drug market. The company also has a leading bio-tech subsidiary active in the European and American markets. The President specializes in R&D strategy. Key responsibilities that come under the President is the management of the drug development pipeline, choosing the optimum portfolio, preparing for and scheduling product launches etc.

Interview 2 was conducted with a renowned Health Practitioner (Expert 2), in the Netherlands whose key interests are digital platform based healthcare and customized patient friendly devices and treatments. Apart from heading a General Practitioners' association, Expert 2 is the co-founder of two companies in the Netherlands – whose primary goals are to develop cheap accessible healthcare for the public. As established in the current theoretical framework, the penetration or market up-take of personalized medicine (at least in the initial phases) will significantly depend on its acceptance by medical professionals as much as it will be dependent on its developers (pharmaceutical/biotech companies) Hence, an external opinion will be quintessential to validate the Personalized Medicine Strategy.

Interview 3 was conducted jointly with two co-founders of a Dutch Biotechnology company (Experts 3 & 4). The company specializes in developing predictive models used to accelerate the drug discovery process. These models which can be used for cardiac drug discovery are one of the many advanced technologies that are revolutionizing the drug discovery and subsequently the drug development landscape. The key reason as to why this bio-tech company was selected is that such predictive models actively assist in personalizing medicines. These models allow to simulate studies of drug interaction with human organs without actually using human subjects and can be customized according to the different organ shapes, disease phenotypes, cell types etc... The interview elements will focus on Personalization mechanisms, possible barriers and assessing the possibility of a mass level personalization.

Interview 4 was conducted at a multinational Pharmaceutical company with headquarters in the Netherlands. The company has a focus in the European market (for drug development collaborations with research agencies as well as formulation), Asia-Pacific and the Latin American markets (predominantly for contract manufacturing of API and formulation.) The interview was conducted with the International Marketing and Sales Manager of the company. Expert 5 is also responsible for designing and implementing Market access strategies and managing external research and manufacturing collaborations with partner companies.

Interview 5 was conducted with the Head of New Chemical Entity division (Expert 6) of a pharmaceutical company. The expert's previous key roles and responsibilities lie in selecting target candidates that can be taken to the drug development phase. The current roles of the expert include API (Active Pharmaceutical Ingredients) and complex generation and also choosing what products go ahead towards commercialization by working in sync with the patent department of the company.

The transcripts of the audios for all interviews will be generated by using the smart transcription software called Otter. These transcripts will be then edited manually for corrections. The results of the data analysis are expected to bring out hidden patterns and relations across different domains of the industry.

Data Analysis Methodology:

In this section, the methodology for data analysis used in the research is described. Since the study involves collection of facts, opinions and views cited by the expert interviewees, a systematic approach to recognize patterns in the data is necessary. If a systematic approach is not undertaken, the research can be viewed as simply a collection of vaguely assembled subjective views with no additional insights (Frechtling & Sharp, 1997) . The step wise breakdown of the analysis methodology is described below.

- Data Reduction: It often occurs that data which is relevant to a researcher is scattered throughout an interview transcript or is dispersed in a different scientific research paper relevant to the researcher's study. This step is done to reduce and reorganize the data obtained after the data collection stage. According to (Frechtling & Sharp, 1997), "Data reduction refers to the process of selecting, focusing, simplifying, abstracting, and transforming the data that appear in written up field notes or transcriptions." In this study, data analysis is done by using the coding and categorization. This step is done separately for the primary and the secondary methods of data collection. But for both, the primary and the secondary data, first codes were generated. The entire process of data reduction was done manually. The codes are basically tags, phrases or words that are assigned to explain a phenomenon in brief. For getting insights from literature (scientific articles, documents etc.) the unit of coding selected were paragraphs. This means that each paragraph was scanned and then a list of phrases describing the essence of the paragraph were developed. These phrases were then classified into 'categories' – Each category serves as a mutually exclusive but exhaustive block of codes which, if put together summarizes the scientific document which is analyzed (Sekaran & Bougie, 2016). Consider, as a hypothetical example, a paragraph from a scientific paper giving information on the following:
  1) How the transition in R&D strategy took place over the last 10 years.
  2) Some innovators (top pharmaceutical companies named A,B,C) started to incorporate biomarkers (P,Q, R) in their research.
  3) A list of therapeutic areas (call them W, X,Y,Z) and whether they are in critical need of a new drug or not.
  4) A brief description of collaborations in the form of mergers and Licensing used to achieve such a transition.

  Then the list of codes and category will be formulated as:

Uncategorized data from Scientific source ----- Paragraph 1	Meta Data	Codes	Category
	W ---- C (stands for critical) X ------ NC (stands for not critical) Y ------- N/A (no information available) Z ---- C (stands for critical)	Therapeutic areas	Transition of Research & Development Strategy
	External: 1) Merger (M) 2) Licensing (L)	Collaboration	
	Company vs Biomarker A ---- P B ---- Q C ----- R	Type of new initiatives undertaken by company profile	

Table 1: Forming codes and category

Next, an elaborate trend assessment is done on each obtained category by marking the differences across two different time periods. In the context of this study, a trend is defined as the general direction assumed by a category representing an industrial phenomenon. To understand the meaning of trend assessment, consider the previous example. The first question to be answered is whether a significant observable change in the state of a category has taken place or not across two different time periods? If the answer is yes, then we move to the second step which is identification of two states of a category. The direction of the identified category or industrial phenomenon is from a 'conventional drugs-based R&D (State 1) to a biomarker intensive R&D (State 2)'. This is how a trend is identified. Similar trends are then grouped under a bigger label to achieve a more cogent display of findings.

Analysis of multiple scientific documents, reports, articles, books etc. generated a list of trends. The same procedure is repeated for the preliminary analysis of the expert interview transcript as well to identify a list of trends that may not have been mentioned in the literature or may not have been acknowledged explicitly by the expert. These trends which are identified implicitly via data analysis are then added to the main list of trends which have been identified explicitly by the experts or mentioned in literature.

Relational Analysis An interrelation in this study is said to exist when two or more trends are observed to move in the same direction in the natural setting of the industry. By natural setting of the industry, it means that the observations and analysis are made in a non-contrived setting. For identification of inter-relation amongst trends, two approaches are undertaken. The first approach includes identification of interrelations explicitly stated in literature and by experts during interviews. This is a straightforward approach. The second approach undertaken was to identify implicit interrelations of trends from literature and views of the experts. For identification of interrelations implicitly, consider the following example:

Suppose, a hypothetical list of codes and category is defined as defined in table 2 below. Then, the method of finding interrelations between the trend identified from table 1 and table 2 is described by table 3 on the next page.

Uncategorized data from Expert Interview Transcript ----- Paragraph 5	Meta Data	Codes	Category
	Push for Randomized Clinical Trials to (RCT)	Complicated Clinical Trial Designs	Changing Regulatory Environment
	Regulating body EMA ---- (stricter approvals for drugs with incremental benefits) USFDA ---- (New control measures for generics)	Type of new initiatives undertaken by regulators throughout EMA and USFDA	

Table 2 Codes and Categories from an interview transcript

Trend	Change of state of categories	Implications	Similarity in implications	Verification from literature	Verification from experts	Interrelation Identified
T1	State 1 (Conventional drug based) --- > State 2 (Biomarker based)	• Increase in costs • Consulting external organizations for research or manufacturing • Adaptation of new regulatory procedures	YES. Push for novelty from regulators is directly correlated with companies rearranging their R&D strategy. Such a rearrangement increases the costs for the company in terms of drug development but will also enable public access to new treatments and drugs and thus greater profits in the long term.	Yes/No	Yes/No	YES. Shift in R&D strategy towards biomarkers is interrelated with tightening regulations by EMA and USFDA.
T2	State 1 (Relaxed Regulations) --- > State 2 (Highly regulated environment)	• Increase in out of pocket clinical costs • New investments for generics and mildly improved version of drugs are less likely		Yes/No	Yes/No	

Table 3 Identifying Interrelations amongst two trends

After all trends and interrelations were identified, they were used to assess the extent to which personalized medicine could fit in the current pharmaceutical industry.

Confirming or cross validating the findings – At each stage of the analysis phase, a cross verification approach or a 'source triangulation' approach was used (Sekaran & Bougie, 2016) In this approach, the findings from different sources are superimposed on each other and the differences and similarities are noted. For this study, it became easy to do that since preliminary analysis of scientific literature was completed before starting the expert interviews. Note that due to time constraints

faced during the research, there might be a select few interrelations or trends which could not be verified by experts or by literature. However, the rationale behind such inferences and indicators pointing towards those inferences have been clearly outlined.

- To summarize, this descriptive qualitative study was planned meticulously. The main research question was broken down into three sub research questions in such a way that the aggregation of answers of the sub-research question are sufficient to answer the main research question. The chapter outlines the scope of the research which guides the subsequent data collection and data analysis methodologies. The primary data collection methodology was expert interviews. The experts were selected after setting a strict criterion based on educational qualifications and industrial experience. This was done to ensure a high reliable quality of primary data collection. The secondary method of data collection was a literature study. The data analysis methodology used was relational analysis for both, literature and expert interview transcripts. A breakdown of the research tasks to answer all the sub research questions is shown on the next page.

Sub Research Questions (SRQ)	Tasks based on Research Content	Chapters
What are the current trends observed in the Pharmaceutical industry?	1) A review of some of the medium/large Pharmaceutical Companies was done to understand what strategies they have already put in place to align commercialization patterns with the market requirements. 2) Four categories of trends were studied. The study began with the understanding of the existing pharmaceutical business model and relevant stakeholders. 3) Next, the influence of patents on pharmaceutical commercialization was assessed. 4) The next task was to identify newly developing public-private transnational collaboration schemes to support the pharma-healthcare sectors. A study of newly emergent market opportunities such as rare diseases was subsequently done. 5) The last task was to study how drug launches are carried out in the recent years.	1, 2, 3,7
What is a Personalized Medicine Strategy? How can Personalized Medicine be commercialized?	1) For understanding the context in which Personalized medicine would operate, first the regulatory framework was understood perfunctorily. FDA and the EMA drafted guides were studied. 2) This was followed by an in-depth analysis of the enabling technologies such as gene sequencing, modern diagnostics etc. 3) The next task was to understand how drug development projects are undertaken and the associated risk factors.	4,5,7
What are the effects of interrelations between these trends?	1) The first task was to cluster trend data into groups/themes based on the part of the pharmaceutical-biotech value chain that is primarily affected. 2) If the trend influence spreads across multiple parts of the value chain, it would be categorized as a major influencer. Subsequently, increases/decreases/ changes in value generation by concomitant variables was assessed by studying the trend data associated with the major influencers. 3) The third task was to compare and contrast the interrelations listed by the experts with those obtained from the literature. 4) A cohesive list of trends along with the degrees of importance and interrelations was prepared.	6,7
What are the risk-sharing mechanisms that can be used by the Pharmaceutical Industry to propel the adoption of Personalized Medicine?	1) The concept of risk sharing was discovered early on during the preliminary literature review. Based on the findings of chapters 3-6 and expert opinions, two areas of emphasis were determined. The tasks were to investigate (i) Enabling efficient asset allocation for developing new drugs (ii) The type of multi-party risk sharing agreements that can be implemented	7

Table 4 Distribution of Research Tasks to answer the sub-research questions

Chapters	Content
1, 2	Introduction to the topic & developing methods to perform the research
3,4,5	Findings mainly related to general trends in the pharmaceutical industry, the business environment of the industry operates, introduction to personalized medicine, enabling technologies, applications and scope (Source: Data analysis from literature)
6,7	New trends and inter-relations amongst known trends are identified. Potential for Personalized medicine assessed. (Source: comparative assessments from Expert Interviews & Scientific literature)
8	A reflection on the entire research method is done. Based on the findings from expert interviews and literature, recommendations are developed.

Table 5 Report Structure in a nutshell

3. Key Trends & Implications

This chapter begins with a description of the business model that was the dominant standard across most large pharmaceutical companies globally. Next, the chapter describes the changing landscape of the pharmaceutical industry in terms of their new approaches to capture market value. Subsequently, the chapter states and explains the different trends affecting the pharmaceutical industry. The trends are characterized into the following categories:

- Business Model: Under this category, the reasons for the shift towards a more economically efficient business models are outlined. Maneuvers used by pharmaceutical companies to retain market share are briefly discussed.
- Product Lifecycle Management: The product lifecycle management is defined by (Hein, n.d.) as "a business transformation approach to manage products and related information across the enterprise." Specifically, in the context of the pharmaceutical industry, we focus on extending the market life of a product once, it has already been developed so that a product (drug in our case) has a higher market access without radically altering its properties.
- Collaboration: As described before in the stakeholder map, pharmaceutical companies require multi-disciplinary teams to work on successfully developing new drugs and increasing their market reach. The collaboration trends describe how different types of organizations are coalescing their positions across the pharmaceutical value chain.
- Product Launch: The trends categorized under this section mainly relate to the tactics undertaken by the pharmaceutical companies to deal with market competition. Just as the performance of a drug is essential for its success, a well distinguished product launch ensuring effective communication of that value across all stakeholder groups is equally essential for a successful commercial venture.

Pharmaceutical Industry & the Blockbuster: Rise and Fall

Every day, novel technologies to treat various diseases, medical conditions and improve human health are being developed. The expected rate of growth for the pharmaceutical industry globally is poised to have a rate of growth of about 4.9% from $ 1 trillion in 2015 to about $ 1.3 trillion in 2020 (U.S. Department of Commerce & International Trade Administration, 2018). However, the pharmaceutical industry of today faces a considerable amount of risk. While the global revenues are expected to rise steadily, the innovativeness in terms of successful new product launches by the pharmaceutical industry is way below par. It has been observed that the Pharmaceutical Industry roughly follows Eroom's law. Eroom's law in this context is that the number of New Molecular Entities (NME's in simpler words mean newly developed drugs) per billion dollars spent on research and development has halved every 9 years since 1950(Osakwe, 2016).

The Blockbuster Business Model was conceptualized to develop select innovative therapeutics that provided an incrementally improvised functionality than its predecessors.

However, a fully integrated pharmaceutical company (which handles R&D, manufacturing and sales all by itself) is exposed to risk at multiple points across its value chain. This can be proven by the observation that on an average in the pharmaceutical industry, out of every 10,000 compounds that are investigated, 250 compounds enter the pre-clinical testing stage. 5 compounds subsequently are chosen to enter the Phase I, II and III trials, out of which only one is approved by the authorities (FDA) (Hannigan, Mudambi, & Sfekas, 2013) . Furthermore, operational difficulties for manufacturing the lab developed compounds on a macro industrial based plant scale brings in a whole new dimension of complexity. It includes, manufacturing permissions, ensuring product contamination, adherence to safety and environmental guidelines etc.

Hence the rationale behind creating the blockbuster was always to find that one product offering that would cover for other failed prospective drugs and in addition to it still yield a high rate of return (10-20 times the net investment) (Gilbert, Henske, & Singh, 2003). Blockbuster drugs are often the results of a wide scale collaboration between companies excelling at different levels of the value chain. (Hannigan, Mudambi, & Sfekas, 2013) concluded that 87.6% of all blockbusters were finally marketed by the major pharmaceutical industries (major companies in their research are the top 12 pharmaceutical companies of the Fortune 500 list).

In the recent years, there has been an increasing pressure on the pharmaceutical companies to lower drug prices due to government initiatives for affordable healthcare(Spatz, 2010). At the same time, the cost and difficulty to commercialize new drugs has also been rising. According to a study conducted by the Tufts Center for the Study of Drug Development, the life cycle costs incurred from developing a new prescription drug to gaining post-market approval is approximately $2.87 billion in 2013 which is 145% higher than in 2003 (DiMasi, Grabowski, & Hansen, 2016). The major reason attributed to this rise in the cost of drug development is the increase of ‘’out of pocket clinical costs”. These clinical costs are incurred as a result of conducting clinical trials. Clinical trials basically are controlled experimental settings where the effects of a newly developed drug is tested on animals and then on humans. If the tests show positive results for a drug’s capability to act on lab animals, the drug is tested on human subjects. In the recent years, a specific methodology to conduct clinical trials called ‘Randomized Clinical Trials’ is often required to The design of such trials include human subjects in two different randomly allocated groups – Group 1 which is given the actual drug and Group 2 which is given a placebo (a drug that looks like the actual drug but doesn’t contain any active ingredients). The drug – responses by human subjects in both groups are carefully monitored. Only if Group 1 performs significantly better than Group 2, the drug is approved. To conduct such clinical trials, many human subjects are needed. This means that due to stricter regulatory protocols, expensive medical consultations to study drug effects, a higher number of test subjects (in thousands) for clinical trials etc. need to be paid for. Further, on an average only one out of five thousand compounds clear medical trials and reach the drug shelf with the process taking about 15 years(Schilling, 2013).

Number of new molecules approved by FDA (pharma and biotech) per $bn of global R&D spending

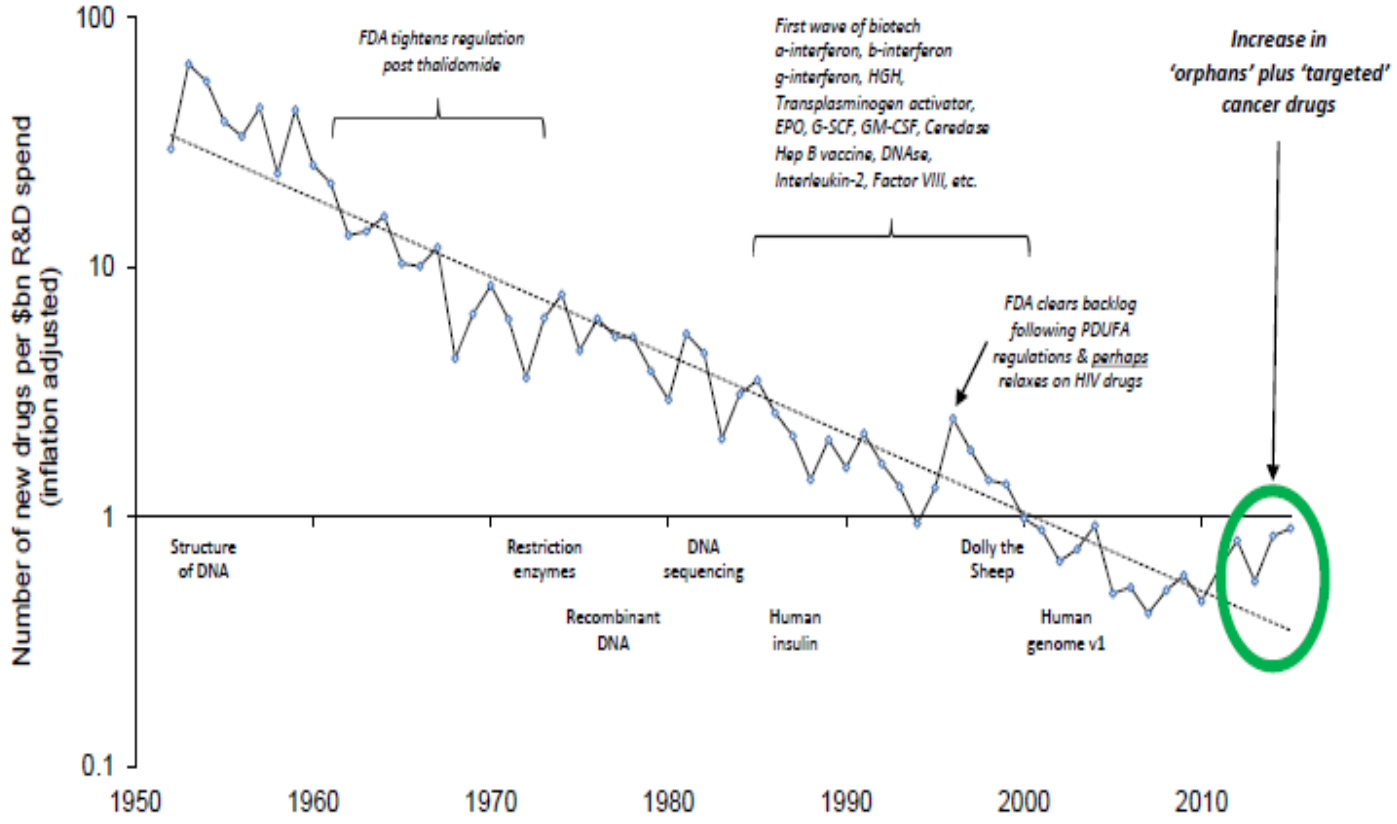

Figure 5 Number of new molecules approved by FDA (pharma and biotech) per $bn of global R&D spending

(Adapted from 'Pharmaceutical evolution: The case for user led innovation' by J. Scannell, 2016, Findacure Scientific Conference, p.5)

To top this pressure up, more and more pharmaceutical companies are nearing patent cliffs which means that the Innovator Pharmaceutical companies no longer exclusively retain the rights to sell the drug exclusively in the market. These patent cliffs are characterized by an instant drop in revenues for the Innovator companies since the huge market share previously acquired by them is now reduced by the authorized entry of various generic drug producing companies(Song & Han, 2016). Generic drugs are identical to the branded Innovator drug in terms of its ingredients, dosage, effectiveness, quality etc. But they are usually priced much lower than their blockbuster counterparts (branded innovator drugs) because they don't have to undergo several clinical and animal studies (one of the most expensive steps in the drug discovery pipeline) (USFDA, 2018).

Creating a chain effect, this market infusion by the generics consequently has put enormous pressure on the Blockbusters to show product differentiation. Now that the medical needs previously met only by the blockbusters are sufficiently satisfied by the generics; an

incremental innovation in the blockbuster drug to gain reimbursement doesn't suffice for the enormous drug development expenses that only the innovators have to bear (Garabedian, 2012). All these problems together mark the end of the blockbuster model and force companies to seek alternative business strategies.

From this section, the key trends that were identified are listed here:

The number of new drugs approved drugs is decreasing despite a multifold increase in R&D spending by the pharmaceutical industry. The associated reasons are increase in drug development costs and stricter regulatory protocols. The increase in costs and regulatory protocols is mainly due to expensive randomized clinical trials mandated by regulatory authorities.

It has become extremely difficult to sustain the blockbuster business model which previously had emerged as the dominant standard for the pharmaceutical industry. The driving factors for this trend are approaching patent cliffs and in turn a high competition from generics.

Connect to the Mass Market

According to the current scenario, the rule of thumb for pharmaceutical companies sequester about 80% of their marketing expenses to get a priority on the prescriber's list. The conventional approach is to capitalize on clinical drug potential and depending upon the countries of sale and regulations, systematic price cut-downs, add on offers etc. are negotiated. The current strategic approach for drug commercialization doesn't give as much importance to relationships with payers, rather it focuses more on giving rebates and discount offers on medications so that they can penetrate deeper into the market (Mozeson & Das, 2010). Furthermore, the current strategy of most established pharmaceutical companies is to improve the efficacy and safety of the drug development and invest more on marketing campaigns for commercial success (Woolmore, Standing, & Wells, 2013).

However, this direct positive relationship between investment in marketing and commercial success has changed significantly. The main reason for this change is the availability of customized re-imbursement plans to patients using specific drugs/treatments suiting their medical needs. This means that the general public has now got options to obtain financial coverage only for specific drug treatments that pertain to their individual health problems rather than paying heavily for an all-inclusive treatment plan (Garrison & Towse, 2017). Hence, excessive amount of market promotions, rebates to health care centers, and campaigns wouldn't necessarily mean that payers would start endorsing a particular drug. The public payers (administrators of governmental welfare schemes, public health funds etc.) strive to keep the health expenses as low as possible. Because of this, the drugs delivering good performance and cost effectiveness in the long term will be prioritized in the payers' reimbursement list.

In the face of increasing uncertainties regarding regulatory approvals, changing market preferences and returns on investment, the commonly recommended pathway for

pharmaceutical companies is to formulate patient and payer centric strategies that ensure continuous access as well as show clearly the comparative clinical and economic value of the prescribed therapy course/ medicine (McClearn & Croisier, 2013). Incorporating economic benchmarks right in the R&D phase of drug development has shown to improve long term market access(JSB Intelliigence, 2005).

Multiple routes of end-product can be analyzed by comparing, formulation safety vs cost efficiency offered for different payer and patient groups after mapping their individual needs, urgencies and the severity of target disease(Woolmore et al., 2013). Another approach that is often simultaneously undertaken is to create joint value ventures with hospitals, third party medical delivery services etc. as well as government sponsored medical agencies (Steibberger, Lucke, Lubkeman, & Juergens, 2013).

The main trend identified from this section can be summarized as:

The conventional approach of securing market share by offering rebates and excessive marketing to healthcare professionals is becoming more and more ineffective. The main reason is a shift in payer preferences to curtail healthcare costs. A need for a payer centric approach is clearly identified.

Product Lifecycle Management by Big Pharma

In order to revive themselves or prevent competitors from cannibalizing their market share, the pharmaceutical industries often resort to the following:

Some larger firms prefer acquisition of generics producing smaller firms and may re-market the same drugs under their brand name (Gagnon & Volesky, 2017) This allows them to spend more resources on marketing, advertising etc. while partially avoiding the clinical trial costs. However, these acquisitions often are hampered by legal issues, back and forth paperwork and operational negotiations. Another strategy that the big pharma often uses is in-licensing products that have reached the later phases of the drug development pipeline, but it often takes up to three years for this process to complete.(David et al., 2007).

Many Big Pharma companies also indulge in 'Pay for Delay' deals which mean that the Innovators pay the generic companies predetermined amounts of money in order to stop them from filing their registrations to start selling the drug. In this way, even after the Innovators have lost their exclusivity, they can still enjoy their monopoly while the generics producer (usually smaller companies) have a fixed income flow and no fear of market competition. Engaging in such deals is perceived as beneficial for both the innovators and the following generic companies. Often, the market followers i.e. the generic producing companies are looking for a periodic cash flows to keep their organizations running efficiently. The average generic price varies for about 6.6 to 66% of the innovator drug in a span of 1-5 years after the first generic has been launched. Furthermore, with market entry of one extra generic, the average relative re-imbursement for that generic drops down by 13% (Vondeling, Cao, Postma, & Rozenbaum, 2018). Hence, the generics are often inclined towards securitizing their own income flows rather than going for a head on collision with the market leaders as well as other generic manufacturing pharmaceutical companies. For

the Big Pharma who are most often the innovators, negotiating periodic payments which are just a fraction of their profits in return for maintaining a near monopolistic market hold seems a lucrative option to exercise. However, off lately, there has been increasing scrutiny on such deals by the trade regulatory authorities in the US and the EU since these arrangements don't promote fair competition and artificially inflate drug prices(Zhang Yunzhe, 2014).

Yet another strategy that big pharmaceutical companies use to revive the market despite losing exclusivity is to introduce Authorized Generics to the market. Authorized Generics are exactly identical in terms of the chemical composition to the original Blockbuster drug, but they are marketed and sold under a private label either via a generic producing subsidiary of the Innovator company itself or via third party collaborations with the Innovator(Hand, 2017). This is the most commonly used strategy in order to maintain a fair market share by the Innovator company albeit at much lower profit margins than previously obtained. The first generics product to enter the market (in the United States - given that it has the required regulatory approvals) after the patent expiry of blockbuster drugs is given a 180-day exclusivity period. During this period, no other firms producing the same generic drug can sell their products, the only exception being 'Authorized Generics.' Because, Authorized Generics originally stem from the same Innovator firms who invented the original blockbuster/branded drug, they can sell their generic version of the products even during this exclusivity period.

A trend termed as the Rx to OTC switch has been increasingly observed in the recent years. Big Pharma companies have started to apply for reviews to re-classify their drugs from a Prescription Drug (Rx) to an Over the Counter Drug (OTC). Doing so gives them a potential opportunity to market their product straight to the end-consumer which isn't possible with prescription drugs(Kumar & Nanda, 2017). For proving that a drug is worthy to be sold as an OTC, the pharma companies invest a huge amount of resources to prove the benefit to risk ratio is considerably high and that wrong usage of the drug can be limited(Fidler & Rebecca, 2016). Usually, pharma companies intend to tap into the mass market of people suffering from allergies and other self-treatable conditions like common cold etc. This is usually done to still maintain the monopoly of the original drug which would have been shattered by the generics.

From this section, the following trends were identified

Large Pharmaceutical companies who had adapted the blockbuster business model apply many strategies to increase the lifecycle of their existing products. This is mainly done to preserve their market shares taking into account the approaching patent cliffs.

Large pharmaceutical companies recently tend to introduce authorized generics once their blockbuster drug expires. This is done to maintain market share, although at less profits.

Pay for Delay deals were a quite commonly used strategy by major pharmaceutical companies. However, due to increasing scrutiny by regulatory authorities on grounds of anticompetitive trade practices, they are less likely to take place.

Rx to OTC switches are commonly used by pharmaceutical companies to directly advertise

their product to the end customer. These switches are only made after thorough scientific proofs of low risk and high medical value are sent and approved by the regulators. These switches allow higher access and generate higher revenues for pharmaceutical companies.

Collaboration Trends

Some big pharmaceutical companies have aligned a part of their new drug development process towards the Open Innovation. This is a phenomenon that was never seen when the blockbuster model was in its prime. There are some prominent examples of collaborations with non-government organizations and academia for the drug development process.

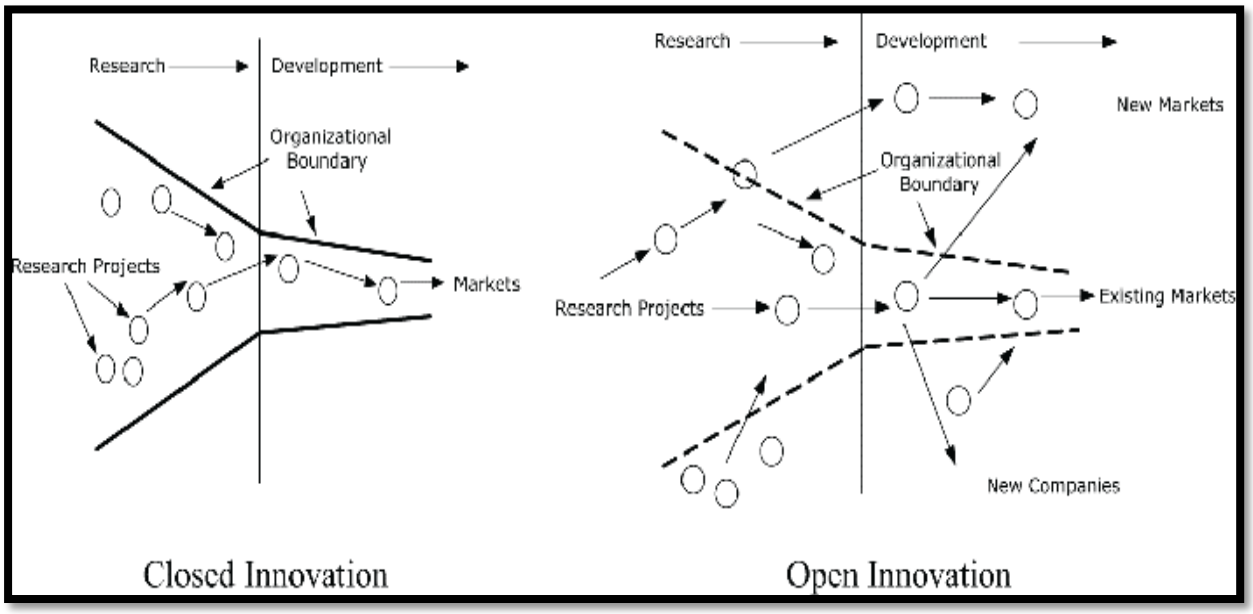

Figure 6 Open Innovation vs Closed Innovation – Schematic diagram

Adapted from Chesbrough 2006 as cited in (Hofman & Niklasson, 2016)

In the recent years, the drug development funnel itself has changed. The stance of big pharma companies leans towards investing in projects yielding guaranteed fixed returns. In order to tackle the problem of investigating probable cures whilst balancing uncertainties of time and money, these big pharma companies often come up with minimum thresholds required for a new drug to be investigated and eventually commercialized. These thresholds might include toxicity criteria, previous research/knowledge base available to develop the compound, reaction pathways, perceived benefits, bioactivity etc. Now, in order to limit the number of new entities that they investigate, more Big Pharma companies have started to use open sourced predictive models generated by academia and bio-tech companies. These predictive models help use statistical data to predict future outcomes. They can be used to quickly narrow down on cheap synthetic routes for drugs, cytotoxicity studies (studies on biochemical agents that are harmful for the human body) and genome mapping (studies focusing on human genetic material) etc. While the scale of such collaborations is often

underestimated, the value they yield over time is exponentially increasing. For example, Big Pharma companies such as Bayer, Merck-Serono, Sanofi, AstraZeneca etc. along with several other small and medium scale enterprises have jointly established the European Lead Factory (ELF) in 2013 by formulating a screening repository of over 300000 different chemical compounds by joining forces with the European Federation of Pharmaceutical Industries and Associations (EFPIA). Furthermore, there are novel incentivization mechanisms rolled out via public and private partnerships recent wherein biotech companies, patient organizations etc. are given proprietary rights in return for pre-defined periodic payments if a compound investigated by them turns out to be successful post screening. Such arrangements have evoked interests from more and more biotech companies to collaborate with Big Pharma in order to expedite drug commercialization. An interesting observation as a result of such trends is that the Big Pharma companies through such crowdsourcing and open-innovation collaborations are transitioning towards a business ecosystem where their over-reliance on highly specialized intellectual property is gradually decreasing. This calls for a major re-structuring of the manner in which products are commercialized currently by most big pharma companies. It becomes likely that for a traditional pharmaceutical company which follows a series of linear R&D, clinical trials, manufacturing and sales approach might have to twitch their business models in order to compete with other more agile industries who accelerate drug discovery via open-innovation and public-private partnerships (Bentzien, Bharadwaj, & Thompson, 2015).

In order to reduce risk of fixed capital, many pharmaceutical companies are increasingly resorting to collaborative Contract Manufacturing Organizations (CMO) in the recent years. Most big pharma companies essentially outsource parts or whole of the manufacturing process such as API (Active Pharmaceutical Ingredient manufacture), formulation and packaging etc. to external organizations with specific know-how to do so. The main reason is since most pharmaceutical products are produced as a result of batch operations, the net profitability of intermediates, API's etc. largely depends upon the scale of manufacturing. Due to approaching patent cliffs, there is a huge boom in the generics production market which are expected to grow at a rate of 6% per annum until 2021. Considering the fact that they capture 88% of drugs by volume, the need to capitalize on production scales has become exigent for many pharmaceutical companies (Bottomley, Hyde, Rangachari, Mekic, & Newrzella, 2017). Furthermore, opportunities have been increasing for CMO's since many large pharma companies who view production of generics as one of their non-core competencies often choose to de-risk and sell off some of their manufacturing capacity to be run independently or at a service cost by external agencies (Cindy & William, 2018). CMO's are often seen by big pharma companies as strategic points of access into new markets which often help in reducing supply/transport costs to the end use (Bottomley et al., 2017) .

Additionally, it has been observed that most CMO's in Europe and the United States, in order to differentiate themselves have started provided integrated manufacturing services. This means that in addition to the API manufacture, these CMO's also perform the next step which is the manufacture of the Drug Product (DP). Previously, this manufacture of DP was largely used to be done in-house by the Big Pharma companies since it is subject to FDA

and/or EMA (European Medical Agency) validation checks throughout the entire process, operational complexities such as need for highly sterile manufacturing environments and most of the times due to Intellectual Property protection issues. Also, the manufacture of the DP is the step that generates far greater value than the manufacture of the API. So, with the changing landscape, Big Pharma companies who often have their manufacturing supply chains sourced efficiently for procuring and processing different raw materials from multiple providers have the opportunity to transition to a different relationship with such CMO's. However, such transitions often have inherent complexities to it. While the global CMO market is set to increase by 6.6% per annum until 2021, exponential growth has been forecasted in select sectors such as Biosimilars, oncology and Highly Potent API's (HPAPI). Nonetheless, the CMO market for generics manufacture is forecast to slowdown in growth despite having the greatest share by revenues currently. The key reason for that is the increasing focus on Biosimilars (specifically in the US and Europe) which unlike traditional drugs are made up from proteins, genetically modified biological organisms, antibodies etc. and are found to be easily administrable, with simple dosing mechanisms. However, the regulatory compliance processes and clinical endpoints for biosimilars are still evolving in the US and Europe because validation protocols are often developed on a case by case basis rather than having a standard protocol applicable to all products. This is because of the fact that biosimilars derived from the same cell types but different source material can often lead to drastically different end products. The interesting takeaway from this techno-regulatory complexity is in the way it might affect collaborative relationships of Big Pharma with CMO's as explained next. As per the global trends, due to upcoming patent cliffs, between 2017 and 2021, approximately 147 billion $ of sales will be lost globally, a sizeable portion of which would be lost by the Big Pharma in the Europe and the US (Bottomley et al., 2017). To combat the potential loss of sales due to patent expiries, these companies need to balance between two major pathways as far as collaborative contract manufacturing is concerned namely:

(i) Expanding production of generic drugs which are therapeutically equivalent to the originator drug in bulk quantities and almost no product differentiation so that short term revenue losses can be minimized, and market share is more or less maintained

(ii) Focus on developing and manufacturing biosimilars which can act as replacements for generic drugs. The major advantage of doing that is the EMA already has specific subsidies allotted to any company involved in biosimilar development. Furthermore, since most biosimilars are so complex to manufacture, the primary preference/tendency of most Big Pharma companies would be to develop it in-house since the biosimilar product throughout all stages of processing constantly needs to be compared to the innovator product called the 'Biologic'. Since obtaining a Biologic which is external to the Big Pharma's R&D involves licensing from other firms, transferring this whole manufacturing, Quality Control/ Assurance process and validation to an external CMO currently seems to be a detriment to faster product launch. Hence Big Pharma companies are still not divesting

their manufacturing facilities in exchange for economy of scale that they might obtain once they collaborate with a contract manufacturing organization. Yet another factor responsible for the Big Pharma's reluctance to scale up rapidly in the Biosimilars is the complete data exclusivity offered by the FDA for 12 years and in case of the EMA for 10 years (Shuster & Farmer-Koppenol, 2013) (Ventola, 2013). However, recent regulations made to promote biosimilars have the potential to incentivize these companies to assume a middle ground and capitalize on outsourcing. One of the examples is that both the FDA and the EMA have drafted guidelines which expedite biosimilars approval with higher priority (Shuster & Farmer-Koppenol, 2013). Yet another very prominent example is the very 'Interchangeability' issue in Europe and the US. Interchangeability in this context means that the pharmacies and some other prescribing organizations could exercise their own discretion to change a doctor's prescription of a 'biologic' to a much cheaper and almost equally effective 'biosimilar'. While the EMA has left this decision to member countries, from the current scenario, the major member countries are likely to allow Interchangeability. A similar situation can also be seen in the US (Ginestro M, 2015). This can serve as a major boost for the biosimilar market and potentially make it viable for the Big Pharma companies as well as their partner CMO's to manufacture biosimilars on a large scale while maintaining their individual profits.

Due to the pressure of dropping revenue losses caused by approaching patent cliffs and a decreasing rate of approved New Molecular entities, it can be determined that market forces, coupled with stricter regulations have led Pharmaceutical Industries to engage in private Research & Development collaborations. Quoting directly from an article published by Pharmavoice, Miguel Barbosa - a Ph.D., VP, head, immunology research and scientific partnership strategy at Janssen Research and Development, "Collaborations tend to be focused on accessing projects across the full R&D spectrum, from new drug targets to late-development assets. But in recent years, R&D leaders have realized that maintaining depth and breadth of state-of-the-art expertise across the complete research platform through the clinical development, the range of activities required cannot be achieved through internal efforts alone" He further went on to acknowledge that portfolio management of risk has also promoted these collaborations ("R&D Collaboration: Thriving in an Era of R&D Collaboration," 2013). This translates to the fact that due to the techno-financial risks involved in the process of drug development, it is much more feasible for Pharmaceutical companies to pool resources even for R&D purposes which pre-dominantly were kept isolated in order to prevent technology spillovers and protection of Intellectual Property.

Significant collaborations between industry and governments have recently been triggered by unmet patient needs and governmental commitment to improve public health. About 30 million residents of the European Union and 25-30 million residents of the United States of America suffer from several different 'Rare Diseases' ("Orphan Designation: Overview," n.d.) (Brewer, 2007)Definitions of a rare disease in the U.S. is a disease effecting less than 200000

or approximately 1 in 1500 people whereas in the EU, it is a disease affecting no more than 1 in 2000 people (Julkowska et al., 2017).

Until recently, it had been a common practice across major pharmaceutical companies across Europe and America to ignore development of drugs catering to Rare Diseases due to demographically scattered end users and highly risky return on investments due to the small scales. While each rare disease targeted individually would be deemed non-profitable from the point of view of a pharmaceutical company, collectively, the portfolio of rare diseases is slowly being a lucrative business prospect. This has only recently become possible due to joint initiatives by the European Commission and the National Institutes of Health in the U.S.A. An extensive network of imaging facility providers, biobanks (repositories that store biological samples), patient organizations, independent SME's gene therapy research organizations as well as healthcare providers have been created to expedite the process of drug developments for rare diseases. With the establishment of the International Rare Diseases Research Consortium as well as the E-Rare program (within EU), more and more pharmaceutical companies are now incentivized to dedicate a part of their existing business towards orphan drugs since many pre-clinical and clinical trials are now fully funded by these programs (which was hardly possible a few decades ago) This cuts off a major risk factor in the drug development pipeline and has started to motivate companies to invest in curing rare diseases (Julkowska et al., 2017).

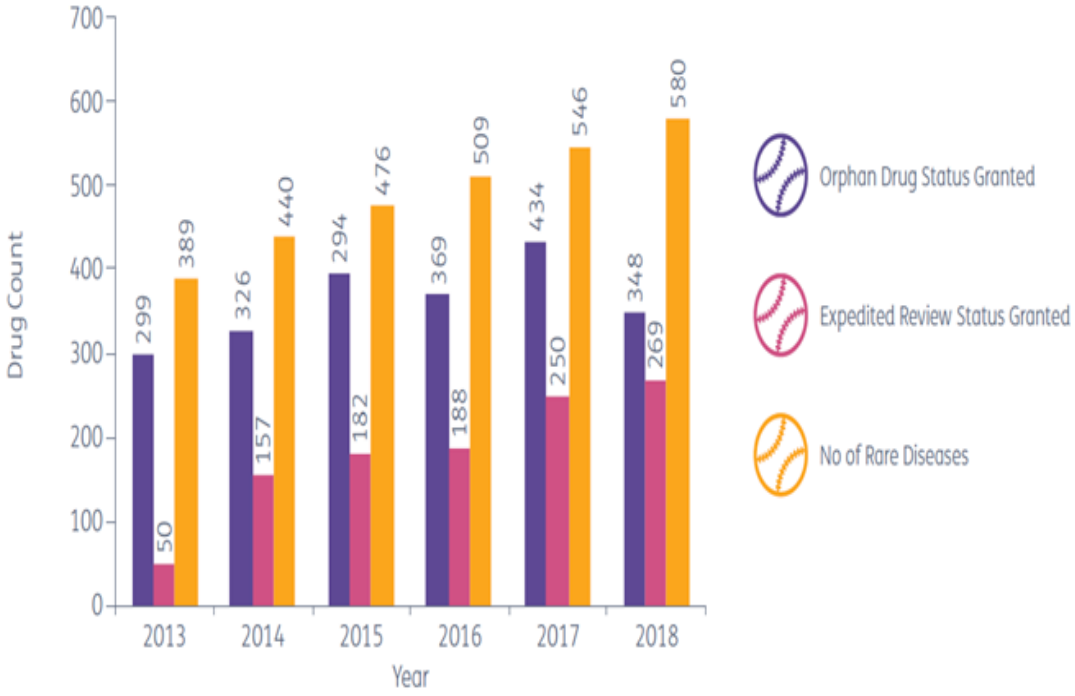

Figure 7 Rise in numbers of drugs receiving Orphan Drug status or an Expedited Review designation and the number of rare diseases under investigation, 2013–18

(Adapted from 'Pharma R&D Annual Review 2019' by Pharmaprojects, 2019, p.19)

Mergers and Acquisitions (M&A's) have always been a key part of pharmaceutical companies. While the top 10 pharmaceutical companies of the world held sales of about 12% globally in the 1980's, this number has largely increased due to the rampant acquisitions of biopharma-biotech companies. The number of such deals made in 2018 was 3003 which was up by 25.5% from 2017 (2392 deals) which was again a rise by 3.4% from the number of M&A's finalized in 2016. An observation from the targets of these M&A deals is that the maximum number of deals were targeted to get novel cures in the areas of oncology-immunology that takes up 28% of the total deals. However, what is interesting to observe is that the second highest number of deals were made with diagnostic companies (Amanda & Steven, 2019).

From this section, we identify the following trends:

There are increasing number of public-private research collaboration initiatives. Transnational collaboration led by EPFIA and ELF has led to the establishment of massive compound screening repositories which can be used to accelerate drug development.

Pharmaceutical industries are very gradually becoming receptive to experiment with open-innovation based business models. This is done to expedite the new drug development process. However, no large-scale implementation is found.

Many large pharmaceutical companies are adapting contract manufacturing rather than manufacturing everything in-house in order to contain costs. Well established generics are increasingly manufactured through CMO's but their growth is expected to slow. For biosimilars and biologics, the manufacturing process is highly specialized, and companies prefer to make them in-house. The fear of technological spillovers restricts companies to go to CMO's especially for biologics and biosimilars.

Incentivization mechanisms in the form of expedited approvals have been rolled out by regulators across EU and the US for companies targeting areas of unmet medical needs. Hence, previously ignored 'Rare Diseases' have received much attention lately. A very high number of merger and acquisition activities are found occurring to resolve the problems posed by Rare Diseases.

Product Launch Trends

As per DiMasi (as cited in Nyhuus, 2014) on an average it takes about 11.9 years to develop a new drug which leads to about 8 years of effective time under market monopoly since patents are granted for 20 years. In such a scenario, the time to market becomes one of the most decisive factors for the survival and performance of the pharmaceutical company. It is observed in recent times that due to increasing budgetary constraints on coverage of expensive medical treatments by governments across the EU and the US, the process of negotiating reimbursements for different drugs has become lengthier and more cumbersome. This means that despite the drug being approved by the FDA or the EMA, the pharmaceutical companies can still not effectively sell for profits unless they receive

authorization from local health providers and even municipalities, insurance agencies etc. is obtained (Nyhuus, 2014).

For instance, in Germany, where this secondary authorization process was automated and products were launched on average within one day until 2012, this process has been replaced by a negotiation process which now takes up to 6 months. As for the blockbuster drugs or any innovator product, every sales day lost under monopoly amounts to a loss of revenues of millions of euros and dollars respectively. It has now become inevitable for pharmaceutical companies to align the clinical efficiency of their products with the relative cost advantages offered compared to their generic counterparts. This has called for a strategic shift from product launches where the pharmaceutical companies were primarily targeting the prescribers – namely the doctors/clinicians etc. to payer-centric product launches. The primary reason for it is the infusion of generics for the common therapeutic areas has created an environment where innovator products offering incrementally higher functionality are completely sidestepped due to their relatively higher costs (Mcclearn & Croisier, 2013)

Furthermore, it has been found in many cases in both, the US and Europe that, payers have started to make their own product assessments and making decisions on prioritizing a product on their reimbursement list. These assessments which are known as Comparative Effectiveness Research (CER) in the United States and Relative Effectiveness (RE) in the Europe. These CER'S and RE's make head to head comparisons in terms of efficacy, lifecycle etc. between available cures and the newly incoming drug/therapeutic introduced by the pharmaceutical companies. This has evolved as a trend given that an unprecedented number of payers in tie-ups with Health Technology Assessment (HTA) groups and Patient Management Organizations have started to establish real world evidence and clinical relevance themselves. This means that, though a product qualifies all the safety, efficacy criteria provided by the regulatory authorities, the product launch by Pharmaceuticals/Biotech etc. directly depends on the outcomes of head to head randomized clinical trials with competitor products. These clinical trials are designed to represent/simulate real world populations and produce results that are statistically significant to the extent that approximate effects of new products can be established. New product launching pharmaceutical firms have to start considering the fact that, while their product was given a go-ahead by the regulatory agencies whose main concern is safety and efficacy of a product, it doesn't necessarily mean that the product diffusion would be equally easy (Moloney et al., 2015).

Another vital trend concerning product launches in the Pharmaceutical Industry related to the interaction they have with the payers of their products. Most payers in Europe and the US have switched their decision making on reimbursement schemes based on outcome-based models. The Big Pharmaceutical companies have the opportunity to capitalize on such a trend by shifting from a largely unit-sales based product launches to more appealing outcome-based product launches. These outcome-based product launches basically offer a guarantee to the payer that the reimbursement price they pay is directly tied to a predefined health outcome of the end user which is the patient (Licking et al., 2016). So, in

order to increase product diffusion into the market via payer acceptance, the pharmaceutical companies have an opportunity to create a risk sharing mechanism by guaranteeing fixed % returns of money or rebates on additional purchases in case of failure to meet patient health outcomes (Seeley & Kesselheim, 2017).

To further strengthen their commercialization process, some companies have also started giving away their payers an independent authority to determine whether the pre-determined health outcome has been achieved or not. Such a shift of power from the pharmaceutical company to the payers was virtually non-existent during the times when the blockbuster was the norm. This creation of a mutually beneficial risk sharing mechanism stems from the fact that a select few payers have now started to calculate effective long-term financial savings in case a disease/medical condition for an average patient is effectively treated versus when a condition relapses and calls for further reimbursement from the payer side. Also, with this arrangement, pharmaceutical companies with radically better products compared to their generic counterparts face relatively lesser threats of being replaced since it would mean lesser copays for patient groups (especially in the US) and pharmaceutical companies would also be able to plan future expansion operations with more certainty since they can closely approximate average sales volumes after a few months of performance observation once these contracts are activated (Seeley & Kesselheim, 2017) .

While, the benefits create an impression of a flawless plan waiting to be executed by big pharma companies, there are certain limitations which hampers these arrangements. In order to constantly monitor change in health outcomes, most pharmaceutical companies as well as payers across the EU and the US would require unrestricted access to the Electronic health records of the patients, associated diagnostic laboratory tests etc. Further, they would need to identify exactly how these results could be translated into a from that can be easily analyzed and made sense of. Furthermore, certain products bring about a change in clinical outcomes over many months and not immediately. So, these arrangements can't be universally applied to all products since neither payers nor pharmaceutical companies might not be always willing to wait and watch in the hopes of securing a probable long-term financial gain. Yet another restrictive factor to such arrangements for drug commercialization is the fact that the discounts or rebates offered by pharmaceutical companies sometimes do not cover the costs of retrieving and processing the data that determines the change in health outcomes. Since most pharmaceutical companies currently delegate this authority to payer organizations, the associated costs also fall on the payer's behalf and thus might prove to be a detriment for effectively commercializing a newly developed drug (Seeley & Kesselheim, 2017).

In this section, the main trends that are identified are:

The authorization processes have become more complex recently. Despite regulatory approvals, in some countries, secondary authorizations from local health providers or in some cases from municipalities etc. are needed. This affects the product launch adversely since every day lost in sales means millions of euros of revenue is lost.

Payers are increasingly found to base their drug reimbursement decisions on the results of Comparative Effectiveness Research/ Relative Effectiveness research. This has led pharmaceutical companies to incorporate cost effectiveness of their product as the most important parameter. In turn, Pharmaceutical companies are increasingly changing their product launch campaigns from a unit sales model to models proving positive outcomes in public health. Due to this, pharmaceutical companies incur more costs, but if they succeed in proving their product's worth to the payer, the profit window is huge.

Trend Number	Short Summary of the most important trends - Preliminary list
1	Decrease in number of NME's approved despite increase in R&D costs
2	Switch from blockbusters to alternate business models
3	Conventional marketing approach is rendered ineffective
4	Pay for Delay deals are decreasing
5	Rx to OTC switches are increasing
6	More number of international public-private collaborations to identify lead compounds
7	Increasing focus on Rare Diseases
8	Integrated Pharmaceuticals are relying on CMO's
9	Merger and Acquisiton activity relating to oncology deals is increasing
10	Payers are demanding cost effectiveness in addition to drug efficacy

Table 6 List of most important trends

4. The Personalized Medicine Trend – Is it the way to go?

Emergence & Concept

In an industry rattled by massive time and economic uncertainty for new drug launches, the focus is now shifting to new methods that involved lesser number of trial and error iterations to get the right product(Mathur & Sutton, 2017).

Personalized medicine is hailed as one of the most revolutionary scientific breakthroughs in the Pharmaceutical/Biotech industries. Put simplistically, Personalized medicine uses information about an individual's genes, environment, response characteristics etc. to either prevent or prescribe treatments for particular medical/disease conditions (Redekop & Mladsi, 2013). Personalized medicine depends upon predictive analytics in order to achieve its final goal which is to improve health outcomes. Predictive analytics are algorithms designed to find patterns and correlations in large data-sets and use historic statistical data to predict a future outcome. The concept of Personalized medicine in contrast to the traditional drug treatments views diagnosis as only one of the intermediary steps in improving health outcomes. The major focus of Personalized medicine is to treat patients free from side effects resulting from intake of various traditional synthetic drugs and also predict the occurrence of certain symptoms/diseases well in advance that it can be completely avoided.

However, knowing that every individual has a different set of immune, metabolic responses, genes etc. the decisive criteria to develop Personalized medicine is to determine the level of personalization that needs to be offered. It means that, while a treatment or a drug can be called as a completely personalized solution if all individuals are given different versions with appropriate modifications, it is not economically and operationally feasible to personalize to such a micro level. Hence, the approach taken by Personalized Medicine developers is that of developing biomarkers for group wise stratification of patient populations (Eppinger et al., 2011). A personalized medicine basically works by profiling a mass of patients into smaller groups based on the similarities of their gene/cell-based diagnostics. Specific treatments are administered by identifying unique characteristics of each group rather than administering a less effective all-in-one version of the drugs to all groups. This detailed profiling of patients wasn't possible earlier until recently, with great successes in the Human Genome Project (Esplin, Oei, & Snyder, 2014).

Pharmaceutical companies have a strategic motive to invest firm resources for giving tailor made cures – Product Differentiation. It works two ways. It allows doctors to confidently prescribe medicines based on the patient profiles, thus removing undesired side effects of conventional therapeutics. The patients who were at the end of the value chain initially, now become actively involved in directing the research of personalized medicine. As more and more patient response data points will be stored in the form of Electronic medical Records (EHR), centralized biobanks (repositories of human genetic samples) would help stratify future patients and their respective cures more accurately(Pulley et al., 2017)(Mathur & Sutton, 2017). Payers will be incentivized to support these initiatives since

this approach leads towards preventive care (ability to stop future illnesses by early detection) which means lesser reimbursements in the long run (Ayers, 2010).

Any strategies prescribed to a pharmaceutical firm to expand personalized medicine to the masses must be formulated considering the context of the current operational models of the payers, regulators, health practitioners etc. For example, before developing any new personalized medicine strategy involving investment worth millions of dollars or collaborating with healthcare providers, several factors need to be assessed such as: Assessment of possible risks vs potential value, Payer readiness to reimburse, scientific consensus regarding the validity/functionality of the personalized medicine, means/infrastructure for necessary R&D, regulatory protocols and their costs, market adaptability and readiness, fit with the company's current services/products etc (McClearn & Croisier, 2013).

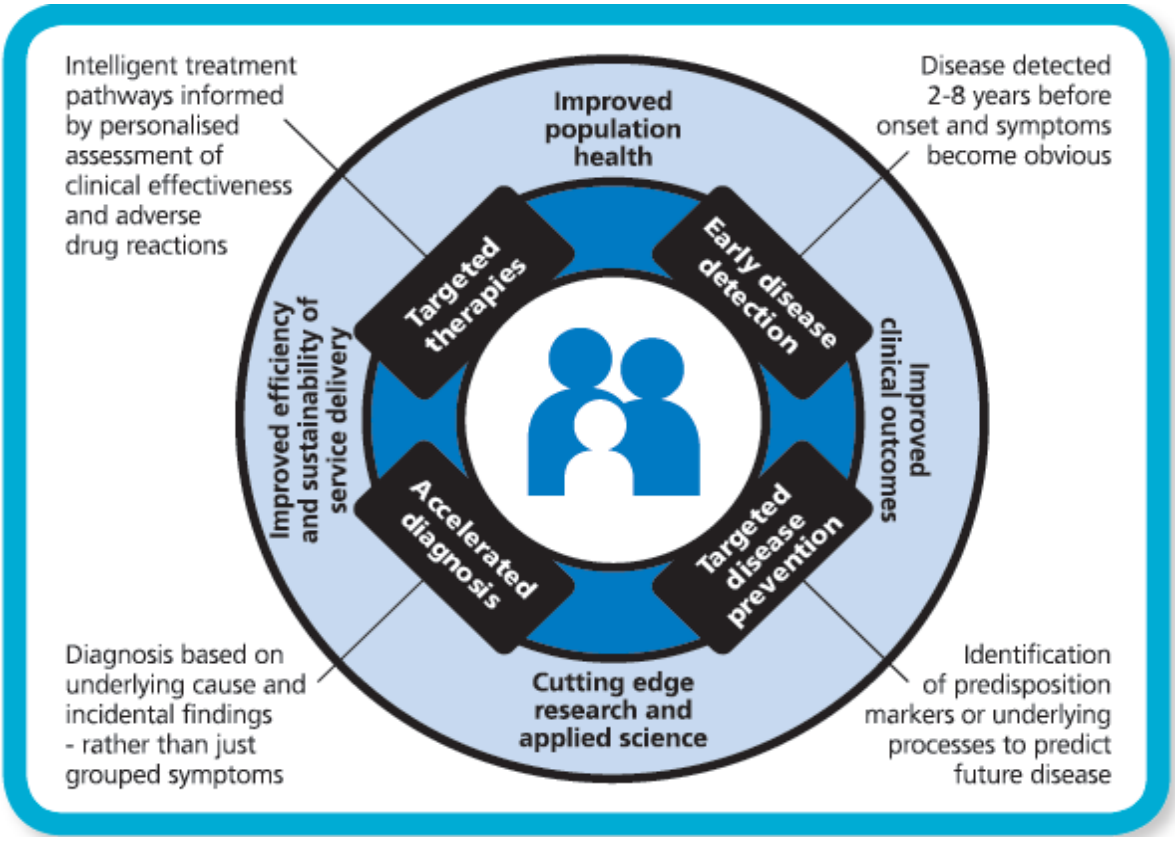

Figure 8 Personalized Medicine Approach

(Adapted from 'Improving Outcomes Through Personalized Medicine' by NHS England, Medical Directorate, Medicines, Diagnostics and Personalized Medicine Unit, Ellen Graham, 2016)

Key Trends Identified from this section:

Instead of the conventional approach where a single drug was designed for all patients suffering from a medical condition, a new approach is adopted. Patients are separated into profiles based on their specific genetic/cellular characteristics. Predictive analytics aid in achieving accurate profiling.

If pharmaceutical companies can commercialize drugs and tests based on this new approach, they have a tremendous opportunity to differentiate their products from the rest of the market. As information from a greater number of end-users will be revealed, the results of predictive analytics will become more accurate. In turn pharmaceutical companies will be able to manufacture tailor made drugs with lesser side effects.

Enabling Technologies

The widespread interest of big pharmaceutical companies to possibly pursue personalized medicine has been due to two major technological advances in addition to Imaging & Diagnostics, and Evidence-based medicine. They are: (i) Genome wide association studies (GWAS) and (ii) Next generation sequencing (NGS) (Whitcomb, 2012).

The GWAS is an experimental framework used to determine a particular trait in human genes. Upon analyzing genetic data of large patient populations, correlations and associations with phenotypic differences are made. It also gives fairly accurate predictions about associated risks from a disease or a particular environment (Visscher et al., 2017). The only drawback to GWAS is that as disease complexity increases, millions of samples need to be processed which increases the initial investments exponentially. The NGS on the other hand, costs lesser than the GWAS, and uses massively parallel or deep sequencing of data and has an advantage over GWAS since it directly identifies the disease causing genetic variants rather than identifying biomarkers that sometimes may not accurately reflect the To elaborate how exactly these technological advancements, interrelate and give rise to a personalized medicine approach, Consider an example of a cancer tumor in a patient's body. Due to improvements in imaging techniques, it has now become much easier to generate and process images of malignant tumors at different stages. With the help of GWAS, genetic data from a huge number of healthy patient populations can be compared with those having the same cancer tumors at different points in time. With the help of Next Generation Sequencing (NGS) techniques, the causal genetic variants can be narrowed down on and drugs targeting those specific variants can be targeted (Whitcomb, 2012).

However, it must be acknowledged that this is a very simplistic explanation of very complex processes. Some of the associated technological complexities are there is often little consensus amongst scientists regarding the best possible pathways to develop and commercialize personalized drugs. This is also because of the fact that certain indicators on which the dosages, toxicity, potency of personalized drugs are based on, namely the biomarkers often are a subject of contention amongst the scientific community (Agyeman & Ofori-Asenso, 2015).

Key trend identified:

Technologies like Next Generation Sequencing and Genome Wide Associated Studies have recently been developed. They enable an accurate prediction of drug interaction with the human body. Although these technologies are still evolving, the potential they have shown to personalize drugs is unprecedented.

Market Prospects and Challenges

In this research, focus will be given on the market prospects and challenges of developing and commercializing personalized medicine from the point of view of the Big Pharmaceutical companies. Despite personalized medicines having tremendous potential to alleviate long term reoccurrences of certain diseases, the Big pharmaceutical companies often are skeptical to invest a sizeable portion in diagnostic tests that characterize personalized medicine because no concrete evidence of long-term financial cost savings can be put forward in front of the payer organizations. Furthermore, since personalized medicine is still in development, most tests that have been commercialized are individual diagnostic tests which are relatively inexpensive. However, for a payer who has guaranteed to cover all medical expenses for a patient, it means that the payer has to pay for many such individual diagnostic tests. Also, this doesn't necessarily mean that the payer saves money despite the likelihood of an accurate diagnosis increasing. While paying for multiple tests might be helpful for the payer in the long run but the upfront costs to experiment, observe and analyze the net health effect might act as a barrier to payers endorsing the use of such tests. Hence, it becomes imperative for the pharmaceutical companies to align their interests with partnering diagnostic firms as well as payer preferences (Davis et al., 2009).

Another challenge to the development of personalized medicine is the absence of hard protocols which must be followed if previously undetected anomalies are found during the diagnostic tests. The market take-up of the personalized medicine also depends upon the method of administration, its synergy with coupled therapies and drugs for simultaneous treatments of other symptoms/diseases suffered by patients. Hence, there are still chances that although a drug produced by a pharmaceutical company is perfectly efficacious, safe, with desired functionalities and tailor made for a strata of patient groups, it still might not work up to the desired level (Davis et al., 2009).

From the perspective of big pharmaceutical companies, the biggest decision is often to balance the molecules that are already existing in their drug development pipeline with that of personalized medicines. It might also happen, that developing personalized cures in a market segment which is already dominated by their traditional therapeutics could cannibalize their own market shares.

Spinning in Favor of Personalization - The case of Herceptin

Big Pharmaceutical companies also have ulterior motives of choosing a Personalized Medicine Strategy other than improving disease diagnosis, lowering costs and identifying risks. As counterintuitive as it sounds, there have been a growing trend where companies have used complexity in identifying biomarkers and patient groups to approve drugs that may not have been traditionally approved by the regulatory agencies. For example,

Herceptin - a drug developed by Genentech to treat breast cancer was only effective for about 25% of the total population due to differing strains of the disease. By traditional regulatory standards set for the blockbuster model, such a small target population renders the approval of a drug next to impossible since there will be many more people suffering from unintended side effects than for those who will actually benefit from the drug (A. Kulkarni & Padilla, 2012). To add on top of it, in all patients, Herceptin was found to be increasing the risk of a cardiovascular dysfunctionality (Pray Leslie, 2008). Hence, the regulatory agency would call for a straight reject.

However, with the help of advanced diagnostics, researchers were able to identify a particular protein biomarker called Her2 which was present in the particular patient sub strata that responded to the treatment with Herceptin. Upon further observations, it was found that even in those patients who responded to the drug, the drug worked significantly well with people having Her-positive marker (found in about 15-20% patients with invasive breast cancer) than with people with Her-negative marker. The company used this information and in turn got the regulatory agency (in this case USFDA) to approve the drug only for the specific patient sub strata which responded positively to the Herceptin drug since in other cases the risk of the cardiovascular dysfunctionality outweighed the possible benefits of using the drug (Pray Leslie, 2008). This could only be done because of accurate diagnostic tests and classification of patient data. So, a drug which could have been easily rejected turned out to be a blockbuster and simultaneously personalized (A. Kulkarni & Padilla, 2012).

Ever since, many Big pharma companies have on select occasions used the power of diagnostics to gain drug approval. Popular examples include drug cures by Elli Lily, Amgen and Merck for colorectal cancer which only worked on patients with a particular genetic mutation in the EFGR gene (A. Kulkarni & Padilla, 2012). However, there is still a huge untapped market potential as to how companies specializing in diagnostics together with pharmaceutical companies can capitalize on these untapped opportunities and even revive old drugs which may have failed in the clinical trials due to side-effect problems, toxicity problems or problems caused due to a statistical insignificance of positive results.

However, an interesting observation from the aforementioned trend is that all products which were tapped in by Big Pharma were in the oncology drug division. The primary reason for it is because of the chronic nature and common occurrence of cancer which in a way leads to treatment via long term therapies and not one-shot treatments. This may be significant for a Big Pharma company making Personalized Medicine, since payers who might not be willing to experiment with established one-shot treatments might be more incentivized to cover personalized medicine-based treatments when they see a potential cost advantage of having to reimburse patients with chronic ailments fewer times than previously required. This suggests that while Big Pharma companies would not be willing to instantaneously personalize all existing therapeutic domains, a lucrative avenue to start research is chronic illnesses.

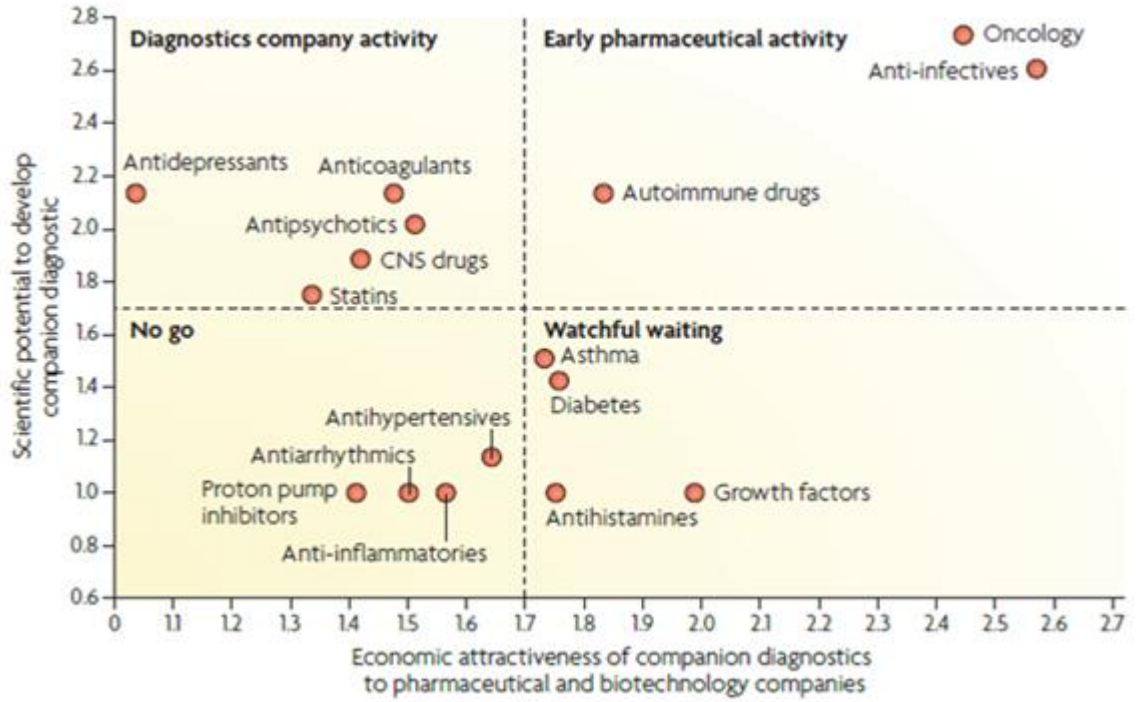

Figure 9 Scientific potential and economic attractiveness for companion diagnostics development across therapeutic areas

(Adapted from 'The microeconomics of personalized medicine: today's challenge and tomorrow's promise' by Davis et. Al., 2009, Nature Reviews, Drug Discovery, Volume 8, p.284.)

Furthermore, it has been found that based on disease heterogeneity (the tendency of the same disease to have multiple mutations causing different symptoms in patients), complexities in identifying disease biomarkers and overall feasibility and economics of relevant diagnostics, the strategic avenues to develop Personalized Medicine for Big Pharma are - the areas of Anti-Infective drugs, drugs targeting Immunology, cardiovascular treatments etc.

Key trend identified from the previous section:

The enabling technologies such as advanced diagnostics and genomics has the potential to influence the regulatory environment in which a drug is approved. If a target patient profile can be clearly identified, then, in some cases, personalized drugs can be approved only for end users belonging to that specific target profile. This can be seen by the approval of Herceptin, one of the most successful and widely used personalized medicine the world has ever seen. This is in stark contrast to the regulatory environment for most conventional drugs, where if a drug doesn't show clinical benefit for a sizeable majority of end users, it is not approved.

Companion Diagnostics – Facilitators of Personalized Medicine?

A key trend that has been observed in the recent years, is the need for Big Pharma companies to start developing companion diagnostics for a successful personalized drug launch. Companion Diagnostics basically are pharmaceutical assays that are developed to determine the correct patient population and responses - they are used as a companion to a specific drug. Often, it happens that the adoption of a personalized medicine is stifled due to inadequacy of data/ commercial companion diagnostic. The reason is most companies only start investing in companion diagnostics after the drug has passed or shows signs of passing phase 2 clinical trials. The reason behind doing so is to reduce the additional risk of investment in case of failure of the drugs (Kulkarni & Ma, 2013). The schematic inserted below shows the position of Phase 2 clinical trials in the sequence of drug discovery and development.

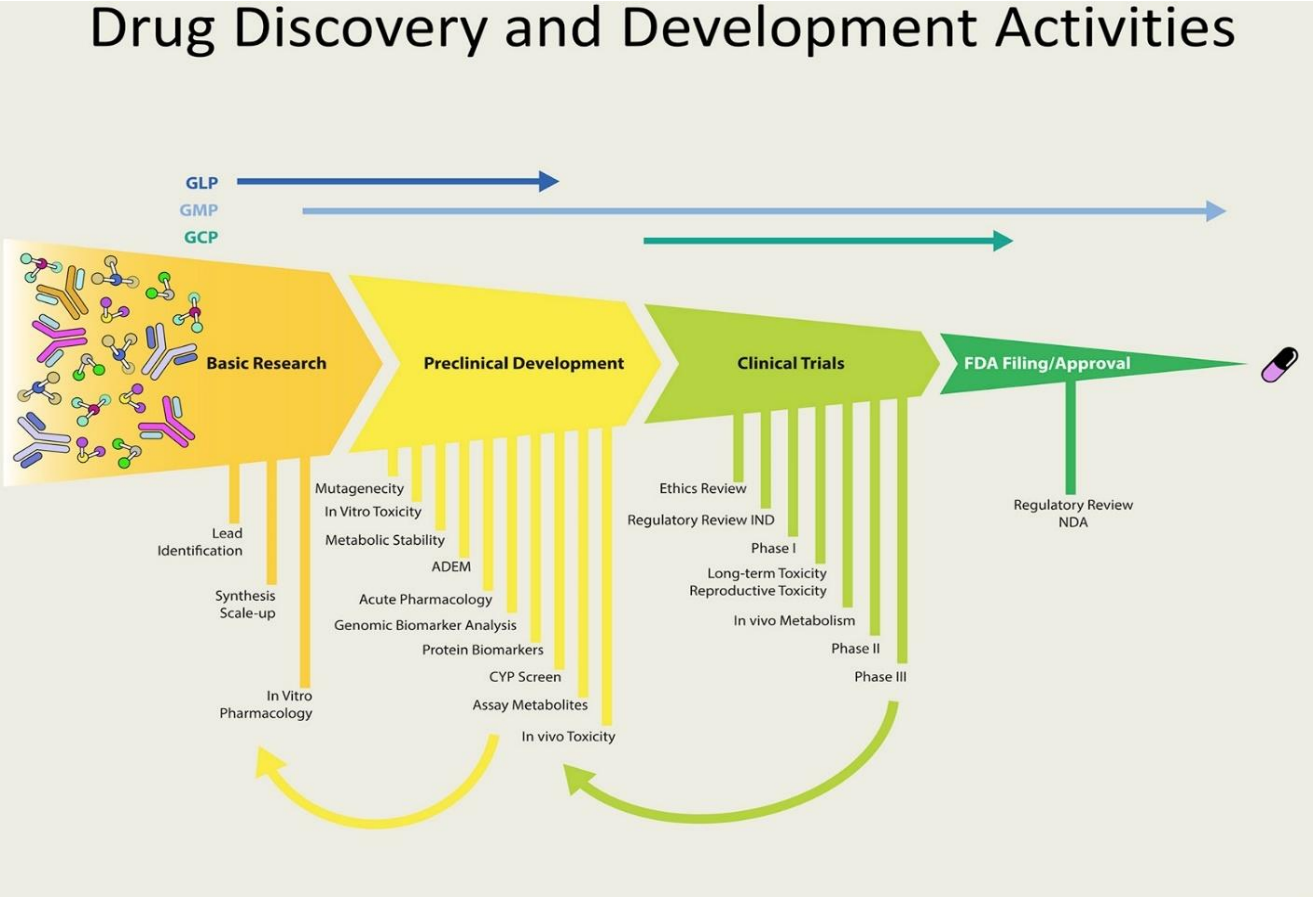

Figure 10 Schematic sequences of Drug Discovery and Development Activities

(Adapted from Drug discovery and development: Role of basic biological research, 2017, by R.Mohs & N.Greig, Alzheimer's & Dementia: Translational Research & Clinical Interventions 3(4), p.656)

The Tradeoff

There lies a huge tradeoff between early investment in companion diagnostics leading to exponentially more market diffusion and delayed investment in companion diagnostics to lower capital risk in case of drug failure. Often, due to the risk averse nature of pharma and bio-tech companies, the companion diagnostic might not be ready for market introduction while the drug itself is ready for launch. The intended outcome of launching companion diagnostics along with the drug is to help medical practitioners establish a common

measurement standard for the tests (Kulkarni & Ma, 2013)s. Furthermore, it has been observed that launching drugs simultaneously with companion diagnostics with the therapeutic allows the pharmaceutical companies to retain a higher drug price in the market since they direct physicians to prescribe treatments with greater precision, thus, obtaining a preferred position on the market (Jakka & Rossbach, 2013).

On the other hand, with a delayed companion diagnostics launch, it leads to setting of arbitrary standards and many a time incorrect interpretation of the results thereby negatively affecting its adoption in the mass market. (Kulkarni & Ma, 2013). It must be acknowledged that pharmaceutical companies are reluctant to go all in with companion diagnostics. This is because in some cases, if there are multiple biomarkers present and it is not known which biomarkers will be predictive, development of companion diagnostic slows down the overall drug development by increasing the population size and costs of clinical trials – the exact opposite of what it was made to do. However, this situation will likely show network benefits with advances in genomic, phenotypic, cellular data collection, storage, mining and processing. Furthermore, while it has been noted that pursuing companion diagnostics in oncology was able to save about 130 million US$ per approved compound, there is lack of supporting economic evidence for other areas. This is because in many cases, the cost reduction achieved by downsizing patient population required for clinical trials is not permitted by the regulatory agencies due to trial validation concerns. It means that, even though diagnostics reduce patient populations required for trials, several biomarker non-responders have to be deliberately added to the trial to confidently generalize (statistically significant) results up to the commercial scale.

Regulatory Challenges to Personalized Medicine – Example - Alzheimer's Disease

Many Big pharmaceutical companies have been trying to research and commercialize a cure for Alzheimer's disease in Europe. Now, it has been a known fact that humans with a particular genotype called 'APOE ε4' are at a significantly higher risk of Alzheimer's Disease than with those with the other common types namely 'APOE ε3' and ' APOE ε2'(Liu, Kanekiyo, Xu, & Bu, 2012). Now as per the Investigation guidelines set by the European Medical Agency, even though this information can be utilized to improve the clinical trials by focusing on such individuals, generalizability of the results to the mass population still needs to be established by including individuals who respond to the identified biomarkers as well as those who don't (EMA, 2014). This means that even though companies have advanced diagnostics will be forced to carry out way larger clinical trials thus inflating their development costs. Disease complexity adds on to these costs. Hence, the net effect has been that big pharmaceutical companies become somewhat reluctant to invest in identifying biomarkers for complex situations.

Key points to take away from the above section:

Pharmaceutical companies willing to incorporate personalized medicine follow either of the following two pathways when it comes to developing companion diagnostics (CD's). Each pathway has its own risk and advantages. The first pathway is early investment in companion diagnostic during initial phases of drug development so that when the drug is commercialized, a higher market value can be obtained by selling the companion diagnostic and the drug together as a bundle. The associated risk is loss of both investments in case of drug failure. The second pathway is a more risk averse pathway. The investment in companion diagnostic is not done until there is a high level of certainty that the drug will be commercialized. In such a case, if the drug fails, the only expense incurred are the drug development costs. Often when the drug is approved, the companion diagnostic is not ready. Hence, the drug is sold standalone in the market until the companion diagnostic is fully developed. This results into a lesser market value of the drug. The pharmaceutical companies partner with companies specializing in diagnostic tests and make the decision.

5. Portfolio Management of Risk in the New Drug Development Process

In the realm of personalization, there have been significant changes in the way drug development projects are funded or valuated. This chapter gives a description of some techniques used to drive drug development projects. The key focus in this chapter is to introduce the reader to the concept of risk reduction: (i) either through application of finance-based concepts or (ii) via working step by step in accordance with the regulatory authorities.

What is Portfolio Management?

Recently, many large sized pharmaceutical companies have started to use portfolio management techniques to reduce project uncertainties. Cooper et al. as cited in (Ding, Dong, Eliashberg, & Gopalakrishnan, 2014) define Portfolio management as "A dynamic decision process which facilitates the evaluation, selection, and prioritization of new projects, and the acceleration, discontinuation, or deprioritization of existing projects in the presence of uncertainty, changing external dynamics and strategic considerations." This basically means that for each therapeutic area, the pharmaceutical companies need to choose and optimize from a multitude of potential drug entities to be investigated. These decisions are made based on many different criteria often in a stage wise manner. Since the drug discovery funnel has a very long timeline up to 16 years, decisions on whether to continue with a project can sometimes only be made after conducting pre-clinical tests or during the stages of clinical trials. Various factors shape these stage wise decisions such as results from pharmacological tests, capital needs of the project vs perceived returns, regulatory approvals, possibilities of scale up for feasible mass production/technology transfer, availability of collaborators, core capabilities/specialization of the company etc. (Jekunen, 2014).

Now, since there is no surety that a project or group of projects targeting a therapeutic area are bound to be successful, in order to decrease the risk, the generally accepted approach is to spread products and research efforts across multiple therapeutic areas. However, the only downside of doing so could be that, because the width of the product pipeline increases, the extra costs and resource distribution across different products might decrease the probability of getting a successful project had all resources been utilized for that one single therapeutic area. An analysis of the biggest Innovators of the Pharmaceutical companies shows that all of them adhere to spreading across multiple therapeutic areas to expand their market reach as well as to neutralize the high volatility of the drug development markets. Projects in areas such as oncology are designed to have an extra clinical trial phase called the phase 0 where trials take place with small scale dosing of the drug to be developed, which enables the scientists to evaluate potential project risks but at much lower costs. Scientists can get a rough estimate general tendencies of drug interaction with human subjects during phase 0 and thus get an approximation of whether a drug is worth pursuing throughout clinical trials or not. (Jekunen, 2014).

Figure 9 below shows that the R&D pipeline by therapeutic areas are dominated by oncology and biotechnology-based drugs (although biotechnology is not a therapeutic area but has been included by the corporate authors of Pharma projects as a separate category to highlight the growing number of bio-tech based therapeutics.)

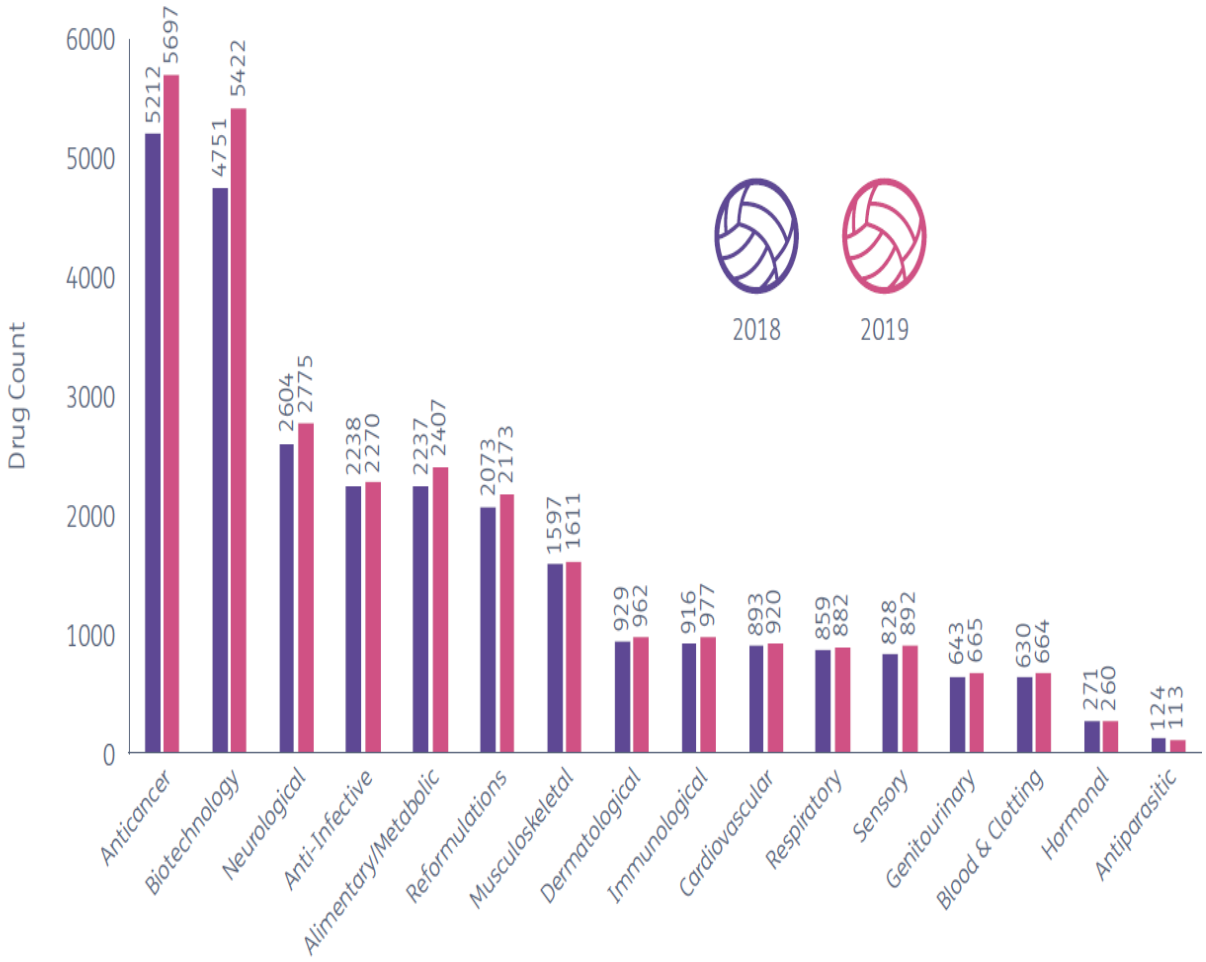

Figure 11 The R&D pipeline by therapy group, 2018 and 2019

(Adapted from 'Pharma R&D Annual Review 2019' by Pharmaprojects, 2019, p.14)'

However, despite having such safety mechanisms, the process of clinical trials is much more complex. Clinical trials are the decisive step in most drug development as well as commercialization projects. Neither do such safety mechanisms give an accurate representation of supposed long term toxicity effects nor do they accurately represent the advantages of the therapy (Bruppacher, 1990).

Furthermore, such phases are often marred by statistical discrepancies. It means that, often the sampling of an inadequate number of participants of a clinical trial is done and results are then generalized for the masses despite not being statistically significant. This statistical insignificance occurs either due to:

1) The extremely small sample size or 2) due to errors in the sampling protocol itself (for example – the sample chosen is not thoroughly representative of the patient groups which are going to be catered by that particular drug). In such a case, even if the portfolio of chosen projects would be ideal, there are chances of inaccurate data creeping into the

decision-making process of an organization. At the end, it may lead to dropping of a potentially profitable product or continuation of a potentially loss-making product.

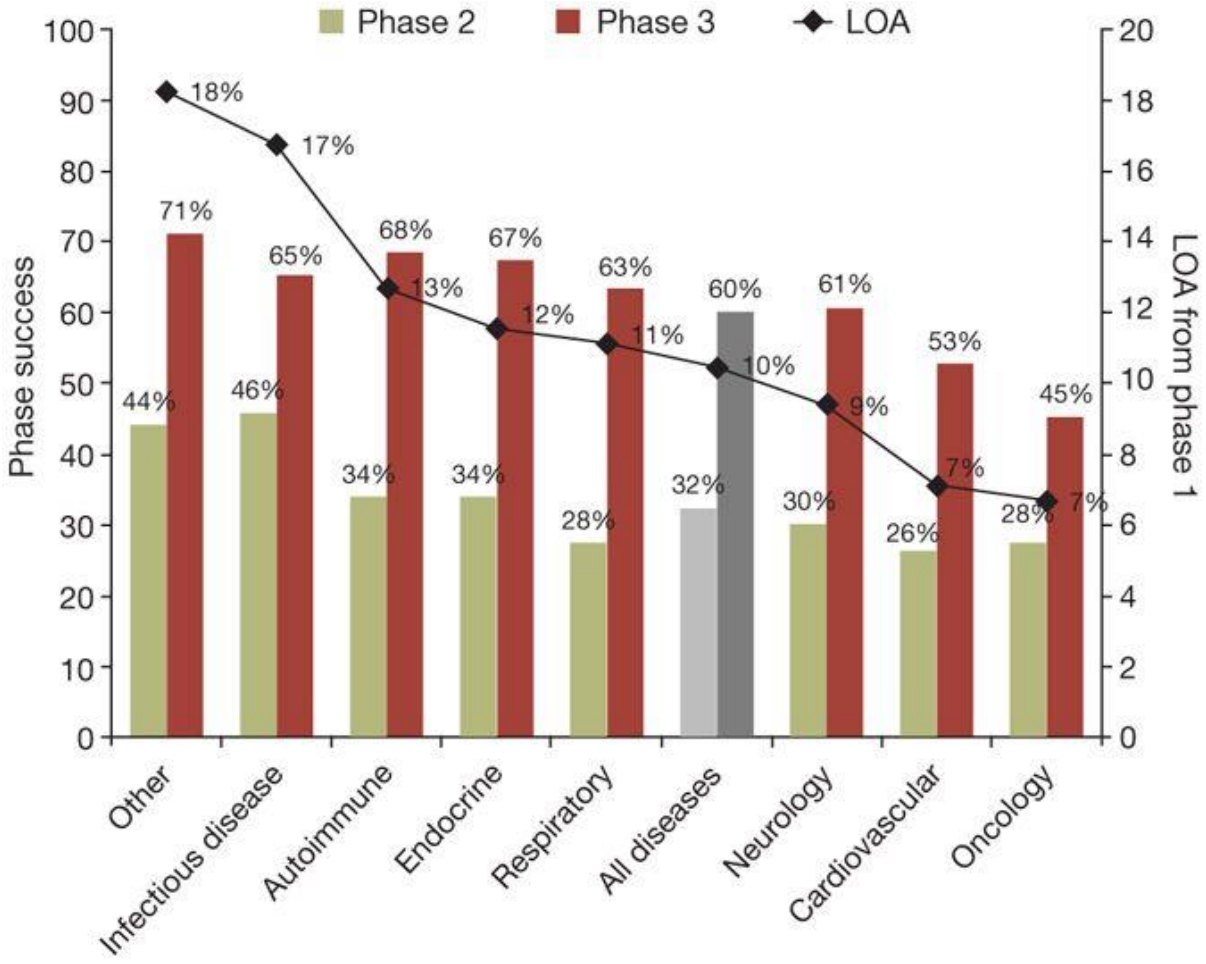

Figure 12 Phase success and LOA from phase 1 by disease for all indications

(Adapted from (Hay, Thomas, Craighead, Economides, & Rosenthal, 2014))

Handling Risks in the New Drug Development Process

In order to alleviate the associated risks, the pharmaceutical industry primarily relied on discounted cash flow analyses which basically incorporates the time value of money and gives a figure for the return on investments or the net present value of projects given that we can approximate the values of probabilities of successes at each mode of drug discovery and development. But because new information becomes available as the clinical trials progress and the future cash flows often depend on various factors outside the control of the organization itself, using this method to valuate portfolio is not reliable. However, it does give a decent estimate of the likely business scenarios. Hence, a lot of pharmaceutical companies and especially emerging biotech companies have started to apply option pricing strategies to portfolios of pharmaceutical products (Ding et al., 2014).

Stock option Pricing models in Pharma-biotechnology industries simulate the trading of financial securities and derivatives by correlating individual projects of a portfolio in the Pharma company's drug pipeline to the volatility of the market (Rogers, Gupta, & Maranas, 2002). To give a little background, options are defined as "Contracts through which a seller

gives a buyer the right, but not the obligation, to buy or sell a specified number of shares at a predetermined price within a set time period (Nasdaq, n.d.)" These contracts are written on an underlying security (Nasdaq, n.d.) which in this case is the potential project that is being planned by the pharma-biotech firm. In the recent years, many pharmaceutical and biotech companies have resorted to use stochastic modeling techniques to incorporate market uncertainty (external parameter) as well as internal uncertainty (for example – low drug efficacy, low cost to clinical benefit ratio etc.) There are many mechanisms that can replicate or give a vague approximation of how the uncertainty can be modeled.

In addition to treating portfolios of different drug development projects as options bound by a yes/no decisions for continuing the projects further, firms have started to account for operational risks of the projects. The portfolio management decisions, in the recent years, have been made by mathematically incorporating a function of various parameters such as market competition (in terms of product maturities/ or relative effectiveness of competitor's drugs), estimated sales generation once the drug is commercialized, fixed or variable milestone payments to third parties or collaborators (for example, expected payments to a biotech company from which a product was in-licensed by a bigger pharmaceutical companies for the late stage development).

Handling R&D - Operational & Regulatory Risks

Very recently, a tool called Target Product Profile (TPP) is often associated to set the context of these decisions. It is in fact endorsed by the USFDA to communicate with the pharmaceutical companies' regulatory aspects, expected drug product specs right after the drug discovery phase. In the European Union, it is called the QTPP (Quality Target Product Profile). The TPP as defined by Steinmetz cited in (Tebbey & Rink, 2009) is "a framework to ensure that the preclinical development program supports the intended clinical trial design and therapeutic use." The TPP/QTPP clearly illustrates how a particular drug in the development funnel will be distinguished from drugs that are already existing in the market place. In order to achieve that, product information right from pharmaco-kinetic data, toxicity, dosages, methods of administrating the drug etc. to final labeling for regulatory approval are plotted. Furthermore, it allows the investigators to validate dynamically the protocols for clinical trials and intervene in a timely fashion if discrepancies are observed (Bode-Greuel & Nickisch, 2008). The target product profile has the potential to completely shift the drug development and production strategies of the pharmaceutical or biotech companies. For example, a change recommended by the USFDA and EMA in the dosing mechanism or mode of administration of medicine could affect the designs and planning of the manufacturing process. For example, consider that by mapping a TPP/QTPP, it is determined that an oral grade drug D will only have incremental benefits compared to similar drugs existing in the market. A pharmaceutical company might then decide to develop an injectable version of the same drug for more bio-absorptivity (more effective once inside the body) and hence a smaller dosage requirement. To produce and commercialize injectables would require a significant upgradation of manufacturing plant machinery and necessitate additional audits from the regulatory departments. It must be noted that such decisions to switch are not linearly dependent on product profiles. They are also heavily dependent on market needs, financial gain (injectable vs oral in our example),

as well as the existing infrastructure and possibilities of technology upgrades. to manufacture the products. Hence, even if product profiles are largely designed to ensure a smooth R&D process, continuously negotiating with the regulatory authorities could directly influence the business strategies and choice of products for commercialization as well.

Variable	Minimum essential	Ideal
Indication	Treatment of HIV-negative children aged 6–24 months and adults with diarrhea due to *Cryptosporidium hominis* or *Cryptosporidium parvum* infection	Treatment of children ≥ 1 month old and adults, including HIV-positive patients, with diarrhea due to cryptosporidiosis. Curative for additional diarrheal pathogens, and safe for use in syndromic treatment of diarrhea.
Product	Single agent or combination drug regimen	Single agent therapy
	Note that the risk of resistance is unknown and may require combination therapy.	
Target populations	Children ages 6–24 months with diarrhea due to cryptosporidiosis	Children ages 1–24 months with diarrhea due to cryptosporidiosis
	Immunocompetent adults with diarrhea due to cryptosporidiosis	Immunocompromised patients with diarrhea due to cryptosporidiosis
		Note that immunocompetent and immunocompromised patient populations may require distinct therapies.
Target countries	Countries that have been shown to have significant endemic cryptosporidiosis or that contribute heavily to the diarrhea burden in children	Countries accounting for 90% of morbidity and mortality due to diarrhea.
Clinical efficacy	Superiority to nitazoxanide in malnourished children	Cessation of diarrhea within 2 days in well nourished, HIV-negative children
	Equivalent to nitazoxanide in immunocompetent adults	≥90% efficacy in all patient populations
		Elimination of the effects of *Cryptosporidium* infection on malnutrition
Microbiologic efficacy	Superiority to nitazoxanide in malnourished children	Elimination of fecal parasite shedding within 2 days of starting therapy for all patient populations
	Equivalent to nitazoxanide in immunocompetent adults	
	Active against both *C. hominis* and *C. parvum*	
Safety/drug-drug interactions	Safe in patients ≥6 months old	Safe for syndromic treatment of diarrhea in patients ≥1 month old
	SAE rate ≤5% by Common Terminology Criteria for AEs; AEs ≥ Grade 2 no more than 30%	No drug-related SAEs by Common Terminology Criteria; minimal drug-related AEs
	No unmanageable drug–drug interactions	No CYP3A4 inhibition; no interactions with antiretroviral drugs
Formulations and dosage	Oral; maximum 3x/day for 14 days; liquid formulation or compatible with hydrodispersible tablet or granules appropriate for children available	Oral liquid or hydrodispersible tablet or granules given as a single dose
		Minimal or no food effect
Stability	≥2 years in Zone IVb (30°C 75% humidity)	≥3 years in Zone IV
Total cost per patient	$US2.00	≤$US0.50 (approximate total cost of nitazoxanide 100 mg/5 ml liquid formulation in India)

AE, adverse event; SAE, severe adverse event

Table 7 Proposed target product profile for treatments for diarrhea due to cryptosporidiosis

(Adapted from (Huston et al., 2015))

Important trends identified from the chapter:

Some of the top pharmaceutical companies have resorted to applying innovative risk reduction techniques in order to handle drug development failures. The use of stochastic modeling to predict market and regulatory uncertainty has been done, although the scale at which it is implemented across the entire industry is very small. Other approach includes diversification of product portfolio to reduce risk, but this is not easy to do since a special expertise is needed to develop drugs in different therapeutic areas.

A simultaneous approach undertaken by pharmaceutical companies is collaborative in nature. Here, pharmaceutical companies work in sync with the regulatory authorities to develop Target Product Profiles and Quality Target Product Profiles. A check mechanism at each stage of drug development makes it easy to identify anomalies and considerably decreases late stage drug failures. This also helps companies produce the required data on drug effects as per the regulatory standards. This is a cost control mechanism that most companies should engage in.

6. A deeper scrutiny: Evaluating Interrelations in trends & Industry readiness to switch to Personalized Medicine

This module of the research tries to explicate the ground reality of pharmaceutical companies today by taking into account key concerns of industry leaders today and their vision of how the industry is changing. A multi-pronged approach will be taken to understand the underlying business-technology complexity, with the interest of actors and stakeholders as the underlying context. The module will contain excerpts from the expert interviews for the trends and interrelations recognized as most important.

The changing R&D landscape (Crowding by generics)

Expert 1 stressed on the increasing timeline pressures faced by generic companies to file applications on the NCE – 1 date. The NCE (New Chemical Entity Exclusivity) according to the USFDA is granted for a period of 5 years. If generic companies, want to enter the market, in certain special circumstances, they are allowed to file ANDA's (Abbreviated New Drug Applications) one year prior to the five-year exclusivity granted to the Innovator companies. The ANDA's are basically challenges to existing patents and require only studies showing bio-equivalence or superiority of the newly filed drug to that of the existing drug (Center for Drug Evaluation and Research, 1998). Expert 1 stressed that (in their experience), now a days there are typically 18-20 companies vying to file applications on the NCE-1 date whereas previously it was just 2 or 3 companies vying to do the same. Expert 1 quoted "This has led to out of court settlements by the Innovator companies and mutual agreements for a common launch date for all of them. They will agree to a date, before the actual patent expiry. But that is at least 8 or 10 years out." So now-a-days, the focus of pharmaceutical some companies has shifted to improving the processes of already filed products - API (Active Pharmaceutical Ingredients) as well as formulation alongside new generics R&D".

From the perspective of Innovator companies, expert 6 comments that the introduction of biomarkers to reduce the attrition rates of clinical trials (in some cases they go upto 90%) is a very important trend that has shaped the R&D landscape. By having better predictive models, the drug discovery process can be shortened. Expert 6 points out that "Gene editing technologies such as CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) and Immunotherapies such as CAR-T (Chimeric Antigen Receptor-T cell) therapies which offer the maximum level of personalization so far, are still at a grass-roots level and is prohibitory for almost 99% of the population. Expert 2 is optimistic about biologics but cautions against blindly switching towards biologics because in his opinion, only after 20-30 years, long term side effects of biologics may start to show.

As for conducting clinical trials, experts 1 and 5 state that outsourcing clinical trials to Contract Research Organizations (CRO's) is becoming more prevalent since most CRO's have the set-up and analysis methodologies ready. Also, their collaborations with patient management organizations give them access to subjects for the clinical trial to take place. Experts 3 and 4 also acknowledge the increasing tendencies of pharmaceutical companies to outsource the pre-clinical stages of drug development.

Key Trend and Contradiction observed:

Expert 1 acknowledges the trend of a changing R&D landscape in the sense that pharmaceutical companies are indeed looking for alternatives to blockbusters. However, the expert rejects the notion that incremental process innovation in drugs is an ineffective strategy. This is in stark contrast with the findings from scientific literature which stated that lesser chances of regulatory approval and payer readiness to reimburse incrementally better drugs make them non-viable investments. In order to comprehend the reason for this contradiction, the source triangulation approach was applied. The expert was presented with the findings from literature and asked to comment on it. The expert quoted that "There are specially developed filing procedures for drugs which are process modifications of a previously established drug. For a pharmaceutical company manufacturing generic, it still has an opportunity to get a 180-day exclusivity as per USFDA regulations if the existing patent is challenged or if the new version of the drug has higher performance/bioequivalence." Hence, it doesn't always make sense for companies with less resources to invest heavily to find a NCE. The expert elucidates that filing for modified generics at the correct timing allows companies to have a decent return on investments with relatively less risk.

Key Interrelation observed:

Experts 1, 2 and 6 also identify a strong interrelation that the switch away from blockbusters due to patent cliffs, infusion by generics etc. is strongly interrelated with more focus on biologics and biosimilars recently.

New Product launches

Expert 1 was of the opinion that due to increasing scrutiny in the European and the American markets for Anti-competition practices, examples or pay for delay deals are going down. Expert 1 added that since the number of companies challenging the patents are increasing, it no longer stays a good proposition for the companies to pay each competitor in order to delay their launch. Hence the inter-relation affirmed here is the decline of pay for delay deals despite the rise in number of generics challenging the innovators. Regarding the effect on the price of drugs due to generic entry, expert 1 comments, "In case of regular oral products where you have at least 15 competitors would say the price would be less than 10% of the brand price, which means the prices erosion will be more than 90%. In many cases, you know, final prize, once the market stabilizes, generics will be just 1% of what the brand price used to be". In more complex products, the price erosion is approximated to be around 60-70%. Price erosion of the products is a function of market competition as well as product complexity." Expert 5 states that evergreening of drugs is a great strategy to prolong market dominance. Evergreening is usually done by innovators in order to extend their patent protection over their high selling drugs. Evergreening is said to have taken place when an existing patent holder files another patent by taking advantage of

legal loopholes or by showcasing very mildly modified versions of the previous patent (Kumar & Nanda, 2017). Expert 5 further points out an interesting interrelation of evergreening with the manufacturing costs. Just by turning an existing drug into a sustained release drug with less side effects and high patient compliance and evergreening the associated patent, companies can have an increased profit margin. Expert 1 also holds a similar viewpoint. The expert elucidates this by taking arbitrary quantities in an example as follows - While improvements necessary to manufacture the new version of the drug increases the total costs by a factor of 1.1, the pricing can be done at 1.5 times or even twice the original selling price of the drug leading to a decent profit margin. Expert 2's views are also in sync with that of expert 5. Expert 2 states that a mere reduction of side effects for statins (lipid lowering medications) and metformin can prove to be extremely profitable at relatively lesser investment in new R&D. By this statement, expert 2 refers to a significant amount of population consuming cholesterol lowering medicines called statins. However, expert 2 states that no initiatives are taken by major pharmaceutical companies to reduce the side-effects caused by statins despite a huge target population. So, if pharmaceutical companies decide to innovate and decrease the side-effects of statins, they would incur incremental research and manufacturing expenses since they only need to modify already existing drugs. In return, they have the possibility to gain massive profits.

Key Interrelations observed

All experts unanimously confirm the interrelation of decreasing drug prices with market infusion by generics. This finding is exactly as stated in literature. But the surprising finding in this regard is that the cost of generics have in select few extreme cases been found to be 1% of the original drug price. In most situations, the price erosion is about 60-70 %. This depicts a very strong interrelation between the drug prices and the market entry of generics.

Yet another strong interrelation was identified between evergreening of drugs with a decrease in drug manufacturing cost. This was confirmed by Experts 1 and 5. In fact, expert 5 also recommended the use of evergreening as a strategy to improve the lifecycle of a drug which is consistent with the literature. Experts 2,3,4 & 6 were not asked to identify this specific interrelation due to time constraints.

The Shifts in business models

Experts 1 and 5 positively validate the finding from the literature review that the new drug pipelines are drying up for the Innovator companies. Citing Roche as the biggest example, expert 1 comments that, the current chemical-based blockbusters are also shifting towards biologics. "Products like Trastuzumab, Avastin etc. are more likely to see less competition and price erosion in the future due to their highly specialized nature and complex manufacturing processes. So, if companies are developing for some very niche oncology, or for very niche autoimmune disease, when the patient pool is not that large, then they

(pharmaceutical companies) are likely to get approval with a much-truncated study design. And also, sometimes they (regulators) allow you (pharmaceutical companies) to keep one or two phases (such as merging phase 2a 2b) as long as there is some phase 4 protocol in place." Furthermore, the side effects profile of biologics has comparatively improved but there is no significant cost advantage that can serve as a motivator to switch to biologics rather than synthetic chemistry-based molecules. Expert 6 also attributes the shift towards biologics, but remarks that biologics are extremely expensive because of the specific nature of research required for genetic/immunology-based modifications. (example - research on monoclonal antibodies is still in its incipient stages) Regarding CRISPR and CAR-T cell therapies, expert 6 comments "The entire business model of bulk manufacturing and bringing drugs to the masses won't apply."

Key Interrelation observed:

The switching tendency of a pharmaceutical company from synthetic chemical-based drugs to biologics is positively correlated with the number of distinctly identifiable niche market opportunities. The deterring factors here are the extremely high costs incurred during switching and sometimes, the high costs of finished products.

This means that if a large pharmaceutical company is equipped to identify distinctly, target patient populations based on specific genetic/cell characteristics, it is more likely to switch to manufacturing biologics.

The Advancement of Oncology over other therapeutic areas:

Expert 1 validates the claim that a major chunk of R&D (about 35% of the new products in the development pipeline worldwide – from literature). Expert 2 also states that personalization currently is largely limited to cancer. Expert 1 further asserts that the increasing interest to pursue oncology products is the direct result from improvements in diagnostics, genomics and peripheral research surrounding oncology. The biggest issue traditionally associated with chemotherapy is the toxicity. So, any attempts to identify pathways to target tumors alternatively through different biological pathways are instantly adapted. Furthermore, since cancer is not specific to one target organ, the number of disease models which can be adapted are maximum. Citing the disease complexity, expert 1 suggests that recurrences of cancer due to mutations always creates an avenue for drug companies to find a cure for cancer. Yet another reason is the severity of the disease. "So, for example, if you want to get a drug approved in chronic disease areas such as diabetes, then your drug should be much, much superior to the other options that are available, whereas in oncology, even if you show a 5-10 percent progression free survival, it is easier to get approval." Citing the importance of companion diagnostics, screening procedures in personalized medicine, the expert gives the following example: If we don't know if a patient is Her2 -ve or Her2 +ve, we would not be able to determine what course of medication to start with, either trastuzumab or eribulin (anti-cancer drugs) or some alternative to those.

Expert 6 adds that areas such as diabetes and cancer are driving the mainstream research primarily due to the number of patients suffering from those chronic illnesses. Introduction of new regulations has also to some extent driven such research across different therapeutic area. For example, the FDA's new regulations mandates the mapping of cardiovascular drugs along with diabetes. So, cardiovascular research is also gradually improving.

Experts 3 and 4 also resonate with the general observation that personalized cures are mainly for cancer because of thorough knowledge of protein targets in the human body. However, due to lack of predictive models for cardiovascular diseases, they state that it is still extremely ambitious for companies to dive into personalization. Experts 3 and 4 strongly recommend involvement of academia to cross these barriers.

Key Trend Confirmed:

Currently, personalization is largely limited to oncology. This trend was confirmed unanimously by all experts and in complete agreement with what was found from scientific literature.

Key Interrelation was identified:

Increasing interests in oncology due to high returns on investments has a direct interrelationship with improvement in companion diagnostic tests. Even incremental improvements in oncology are highly rewarded due to the seriousness of the disease. Hence, companies consider it worthwhile to make early investments in oncology to develop companion diagnostic tests that can be sold at a high price along with the approved drug.

The role of healthcare professionals

According to expert 1, the influence of doctors is not likely to decrease with the onset of personalization since, the entire process of innovating is a feed-back mechanism where every increment in treatment is an outcome of detailed discussions with healthcare professionals and doctors. This is in contrast to scientific literature suggesting that personalization will drastically reduce the influence of physicians and doctors in the decision-making process and involve patients. According to expert 5, the current pharmaceutical marketing model is largely aimed at demonstrating scientific evidence (enhanced safety & efficacy, reduced toxicity) and pricing benefits to doctors rather than to the patients directly. For a drug to be prescribed often, Expert 5 stresses on the importance of long-term relative pricing which means that the absolute price per unit may be higher, but the total treatment duration, costs and dosages of drugs required is lesser than the other existing products. Expert 5 and 2 state that with increase in personalization, they project the dependence of pharmaceutical companies to be higher on doctors', physicians and healthcare professionals in general. This is in stark contrast to some of the scientific

literature which states that patient empowerment will likely diminish the influence of healthcare professionals.

Key Point of Contrast observed:
Scientific literature states that the influence of doctors and healthcare professionals will decrease with the onset of personalization. However, this is another point that was contradictory to the opinions of experts 1,2 and 5. In fact, they suggest the following interrelationship amongst future trends.
As personalization increases, the influence of doctors, physicians or other healthcare professionals will also increase. The experts cited that fundamentally, all scientific evidence generated by pharmaceutical industry are showcased to the doctors. Then, the preferred choice of treatments are made by patients in consultation with doctors and healthcare professionals based on severity of medical condition and the associated costs to treat it. However, increasing personalization means increasing choices available to the patient which means even more necessity to consult healthcare professionals.

Portfolio of R&D products

Expert 1 suggested that the choice of portfolio primarily depends upon the number of API manufacturers, number of existing and potential competitors, the expertise in drug specific areas of chemistry. Citing the increasing need to stay competitive, the expert suggested that bundling products to cover the entire width of the therapeutic area is a great strategy. Even though, one or two new products that a company is trying to develop are not the best in class or priced in the most competitive way, bundling offers a significant advantage over independent products. Bundling refers to selling a group of products as one package. As for assessing the economic benchmarks during R&D, companies whose focus is generics, use relatively simple benchmarks such as discounted cash flows - Net Present Value or the Internal rate of return (rather than quantifying the different types of risks associated with independent projects). According to expert 1, comparisons with economic benchmarks make more sense when the drug enters the clinical phase since that part of the project is the largest out of pocket expense typically for a drug developing company. Option pricing models for pharmaceutical projects are used more in situations where a company is in-licensing a range of products from another company. They are also used if a company has outsourced clinical trials to another external organization and there is a need to determine specific milestones along the project as to what will be the commercialization potential of the products or assessing whether to continue with the project.

The importance of reimbursements

Reimbursement refers to the phenomenon where an end user (patient) is paid the medical costs they incur. It must be acknowledged that if the generics are not demonstrating a significant improvement, then European regulatory authorities often do not permit re-imbursement of the drug after launch. A drug ineligible for reimbursement will not be the likely choice of healthcare professionals since their aim is to contain healthcare expenditure wherever possible. Expert 1 cites the example of a Sanofi product called Zaltrap (a drug to

treat metastatic colorectal cancer) which was denied approval and reimbursement by the European authorities in France and U.K since there were products such as Avastin and cetuximab used to treat similar conditions. The readiness of payers to reimburse are to be considered when formulating the pricing strategy of the drug because there have been cases that the payers (insurance companies), even after drug approval refuse to reimburse a particular drug.

The Impact of regulations on manufacturing new products

Expert 5 states that, in general, stricter inspections of manufacturing sites are carried out as per the standards set by USFDA or EMA or EU GMP ((European Union) Good Manufacturing Practices). An example of one of the very recent trends is 'Serialization.' In the words of expert 5, "It means that, starting February this year (2019), throughout the whole of Europe, all pharmaceutical products, every SKU (stock keeping unit), every box that goes out of the factory, needs to have a unique identifier like a QR code. And this QR code contains all the information about where this product was made, who is it from, what's the expiry date etc." This means that companies will have to develop or get access to information technology systems that have algorithms running in sync with their product packaging lines and transmit this data to the national and European repositories. The main aim of introducing serialization comes as a consequence of the EU introduced Falsified Medicines Directive (FMD)(European Union, n.d.). Expert 5 continues, "This is a big change in Europe. Not all countries have been able to comply with this. Countries like Italy have asked for an extension because they haven't been able to implement the whole system. It's an expensive system - for a product, it will cost at least $50000 to $100,000 to implement the whole scheme. This is another barrier to entry." Expert 5 states that the attempts at international standardization of regulations by the joint efforts of EMA and PICS (Pharmaceutical Inspection Cooperation Scheme) has not produced the best results possible yet, due to differing levels of implementation and infrastructure readiness in different countries. This is a challenge faced by regulatory authorities currently.

Explaining the negative impacts of regulatory pressures, expert 2 states that at present, a sizeable fraction of the 70,000 patients in the Netherlands might not be able to get access to the specific diuretics. Expert 2 asserts that extremely aggressive pricing stances assumed by the regulatory authorities are responsible for this. It makes investments in some therapeutic areas unappealing for the pharmaceutical companies. This is a classic example of market stress being translated to patients and in turn leading to poor overall health outcomes.

Key Trend Identified:
A new trend called 'Mandatory Serialization in the EU' was identified by expert 5. The confirmation of this trend could not be made. This is because no other experts were aware of this particular trend since it falls under the specialized expertise of Expert 5 and because it is the consequence of a new rule implemented across the EU.

Impact:
Serialization is an attempt to standardize all product packaging lines in pharmaceutical industries across the EU. This increases the manufacturing costs per product significantly.

Another interesting observation (specific to the Netherlands in the EU)
Citing the example of regulatory agencies in the Netherlands, expert 2 suggests that in select few cases, stricter regulations can sometimes be counter-productive. Expert 2 states that hard pricing stances assumed by regulators on drugs in certain therapeutic areas often make investments unviable thus creating a gap between demand and supply.

The rise in diagnostics

Expert 6 projects a steady rise in diagnostic companies. The expert illustrates the emerging need for diagnostics in the following manner - In the immuno-oncology field, there was a huge impetus to find drugs that inhibit a particular type of protein binding PD-1/PD-L1 which helps cancer cells to survive the action of the human immune cells called T cells. Now, Merck and Bristol Myers Squibb are amongst the few companies which have developed biologic drugs Keytruda and Opdivo respectively. However, the drugs will only be effective in individuals showing a high expression of PD/PD-L1 and those individuals can only be identified through companion diagnostic tests. But this has a cost implication. Before buying the drug, the individuals will be required to undergo the diagnostic test associated with it. Only those individuals where the expression of a particular receptor target will be treated with the drugs developed. So, this might lead to saving costs on ineffective treatments. Expert 3 attributes the rise in companion diagnostics to a monetary incentive. Expert 3 states that often during the clinical trials, a newly developed drug meets effectiveness targets only for a sub-section of the population. So, in these cases, they are only allowed to go to market if they demonstrate that they will accurately identify the target population. And so, they develop a companion diagnostic

Key Interrelation identified:
The rise in companion diagnostics is directly interrelated with the need to develop personalized drugs.
Motivating Factor: Ability to obtain added sales value is a motivating factor to develop companion diagnostics.

Profitability in the Rare Diseases market

Experts 1 and 6 both held the opinion that, the decision to jump into the Rare Diseases market is more business driven rather than being driven by advances in basic sciences. Since there is very little competition and in free markets such as the U.S, prices can be jacked up without much restrictions. Hence, the increased research and development costs for Rare Diseases can easily be recovered thereby leading to a higher profitability.

Power Dynamics amongst actors and stakeholders

Expert 2 is an external stakeholder to the pharmaceutical industry. Expert 2 claims that while regulatory authorities and payers serve to ensure fair pricing by pharmaceutical companies, sometimes, their influence can result in undesirable consequences. The power positions of the Dutch government and insurance companies to lower drug costs had once misled a pharmaceutical manufacturer to compromise on quality control issues. Due to lack of quality control measures, carcinogens were found in anti-hypertensive drugs manufactured by that specific manufacturer. Experts 3 and 4 identify an important interrelation due to the power position held by insurance companies. They state that insurance companies are in most cases not convinced of the economic viability to reimburse for preventive care. Since, the payers perceive reimbursements of preventive medicines or early stage diagnostics as short-term costs that could be avoided, there is a strong external preference for curative medicines by the payers and this is commonly observed across the Netherlands as well as the US.

Key Interrelation Identified:
The tendency of pharmaceutical companies to switch towards preventive care (early detection, monitoring etc.) has a negative interrelationship with the power position of the payers.

Reason cited:
Often the payers are not convinced about the actual future cost savings if mechanisms for preventive care are developed. Also, there are disagreements between pharmaceutical companies and payers on the types and number of screening procedures that a patient must undertake for early detection and prevention of illness. Hence, the payers are reluctant to offer reimbursements for such mechanisms based on preventive care. This adversely affects the pharmaceutical companies willing to develop preventive care-based solutions.

A regime shift from conventional medicines to Preventive Personalized care

In the words of expert 2, "80%, maybe even more, of the current diseases globally, due to a strict medical condition, but due to your lifestyle. For example, if you look at ketogenic diets, we know that adherence to it plays a role in reversing type two diabetes. In diseases like cancer or cardiovascular problems, the need for novel medicines will remain intact. But I think that lifestyle change will evaporate bulk of the chronic medication." However, expert 2 also projects that going to be a sizeable population that might not respond to lifestyle change advocacy and advanced monitoring mechanisms. The pharmaceutical companies should consider remodeling themselves to target those populations. Additionally, pharmaceutical companies can also remodel themselves by targeting drugs that can act as facilitators for lifestyle changes. For instance, it is a well-known fact that obesity and lipid metabolism is directly related to sleep. So, if companies targeting sleep inducing drugs position themselves as facilitators of these lifestyle changes, then there are many new avenues to capitalize on. Expert 2 also suggests remodeling via developing combination

medicines rather than standalone drugs. However, expert 2 acknowledges that such remodeling with a long-term strategic vision will lead the companies to endure short term financial losses which may be the cause of their reluctance to do so. Regarding personalization, expert 2 states that improved diagnostics are gradually bringing consensus amongst the scientific communities regarding root causes of the diseases. However, personalization on a large scale may still mean that different courses of treatments are offered based on the subjective interpretation of the healthcare professionals. Expert 2 stresses on the need to create an enabling environment to enable this regime shift with integrated data sharing networks and access to clinical data repositories simultaneously since they will directly govern the rate at which personalized medicine is commercialized. Expert 2 stresses on the importance of Med-Tech (medical devices used to collect and transmit public health data in a secured manner) to be a deciding factor for personalization. Experts 3 and 4 point out that personalization is jointly pursued by independent research organizations, biotech companies up to the clinical trials stage and then acquired by the bigger pharmaceutical companies. They further state that biotechnology companies operating via simple fee-for-service models are not seen as an acquisition target in the eyes of the investors. They elaborate that the fee-for service-model of bio-tech companies is primarily developing platform technologies, or organ on chip models and then charging bigger companies to test new drugs for a set price. Such models ensure a periodic stream of income but never a peak in the returns for an investor and hence such companies are not seen as potential acquisition targets. Hence, companies developing personalized predictive models should look forward to switching towards selling the drug assays rather than offering services to a bigger company. Only then, they have a chance of commercializing their product on a large scale.

All in all, expert 1 believes that the enabling environment (genomics/screening/etc.) is not fully developed for a traditional pharmaceutical company to switch towards a business model with a focus on personalized medicine. However, in their opinion, generic companies looking for alternative business models are targeting incremental improvements in patient profiles or changing drug delivery mechanisms (such as incorporating nanotechnology-based products or liposomal products). When they have enough resources and competence, they can switch to innovative or specialty drugs which can further be personalized. Expert 2 projects a slow rise in integrated solutions (drugs + lifestyle recommendations aimed at preventive care) but maintains that personalization is largely limited to oncology at present. Experts 3, 4 and 6 raise concerns regarding cost reimbursements as one of the major challenges to the adoption of personalized medicine. All experts resonate that personalization is the way forward but are highly skeptical whether it will be possible within the coming 5-10 years.

Key points to takeaway:

Expert 6 cites that the most recent gene editing techniques like CRISP-R and CAR-T have shown tremendous promise in the sense that they can enable personalization at an individual level. But currently, these technologies are in their incipient stages. The price

is so high that it is simply inaccessible by more than 99% of the population.
Experts 3 and 4 identify an interrelation that to speed up the commercialization of personalized medicine, sometimes, the biotechnology companies also need to reposition themselves (for example from a fee for service model to sales of drug assays).
All experts maintain that personalization is largely limited to oncology.

Interrelation Identified:

Expert 2 identifies the interrelation that the rate of development of medical device technology, data sharing networks and patient data repositories is directly interrelated with faster commercialization of personalized medicine. This interrelation is in agreement with that obtained from scientific literature.

7. Conclusions & Discussion

In this section, representations of the findings will be done to capture the gist of the research. Subsequently, the future possibilities of continuing this research will be mapped out in detail. Lastly, a new Personalized Medicine based Pharma-Healthcare ecosystem will be envisioned. This vision is partly based on the findings from this thesis and incorporates some specific remarks made by the experts that were interviewed.

For answering sub-research question 1, the trends that were identified in the literature are listed in table on the next page. The trends were grouped together under separate categories which can be found in the 'Type' column. The 'Type' column consists of categories which cover the drug research and development to strategic partnerships; from regulatory aspects to product launch, marketing and lifecycle improvement. An additional category which is added at the bottom of the table is based on future trends that might shape the pharmaceutical industry. A total of 26 different trends were identified and displayed in the table.

For answering sub-research question 2, the trends that were identified as the outcome of answering sub-research question 1 are mapped against each other to create a matrix of 26*26 trends. This mapping is done to showcase the interrelations symbolically and to get a sense of how each trend moves with respect to the other. This table does not provide definite causal relations, but correlations (as described in the methodology). The trends are written as T1, T2…. T26 in the same order as in sub-research question 1. Relative movements of two trends with each other are plotted via different symbols. A small legend at the end of the Interrelations matrix provides the reader the meaning of each symbol which can be translated to the movement or impacts of two trends with respect to each other. If a cell in the matrix has signs + and – both, it means that the two trends may or may not move in the same direction. The movement or the impact then becomes the function of company preferences, core competencies, the market environment, and regulations. If there is no identifiable impact or relative movements between trends, they are marked with a Φ. If there is not sufficient information to predict or analyze the movement of trends, the interrelations are marked with a ●. The table is read as T(row's) correlation with T(column).

The answer to sub research question 3 is presented descriptively after the first two sub-research questions are answered. Finally, all answers to the sub-research questions are merged together to formulate the answer to the main research question.

Answer to Research Question 1: What are the current trends observed in the Pharmaceutical industry?

List of Trends		
Sr. No.	Type	Trend
1	Business Model	Switch from Blockbusters to Niche drugs
2		Switch from vertically integrated Business models to collaborative network based models
3		Gradual move towards incorporating Open Innovation
4	Regulatory	Increasing Pressure on Pharmaceutical and Healthcare companies to reduce costs
5		Lesser Approvals for products with Incremental benefits
6		Adherence to Serialization guidelines across Europe leading to extra expenses
7		Increase in out of pocket spending (for drug development) to adhere to stricter regulations
8	Markets & Product Lifecyle Management	Patent Cliffs causing an influx of generics & Introduction of authorized generics
9		Shifts in payer prefences inducing a change in pharmaceutical market access approach
10		Evergreening strategies
11		Fall in pay for delay deals
12		Rx to OTC switches
13	Collaboration Trends	Public - Private research partnerships between bio-tech, patient organizations & traditional pharma
14		Collaborations with CRO's and CMO's
15		Joint research initiatives by National Institutes of Health (USA) and European Commission
16	Product Launches	Comparative assessments between treatments done by payers themselves to estimate cost-benefit
17	Research & Development towards Personalizaion	Drop in R&D productivity per unit cost
18		Research towards biologics and curing rare diseases
19		Setting novel economic benchmarks in R&D to assess product pipelines
20		Developing Companion Diagnostics
21		Identification of Biomarkers, developing new screening mechanisms for accelerated drug discovery
22		Attempts at developing patient sub-strata using technologies GWAS, NGS etc.
23		Specific focus on Oncology
24	Future Projections	Integrating lifestyle studies and solutions along with drug treatments
25		Creation of megafunds, use of financial engineering techniques to hedge pharmaceutical project risk
26		Improved Risk Sharing agreements & value based pricing schemes

Table 8 : List of trends shaping the pharmaceutical industry

Answer to Research Question 2: What are the Interrelationships observed between these trends?

Matrix showing the effects of Inter-relations between the trends (T)

Read as (T row's) correlation with (T column)	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10	T11	T12	T13	T14	T15	T16	T17	T18	T19	T20	T21	T22	T23	T24	T25	T26
T1	=	+	+	-	-	ϕ	+	-	-	-	+	ϕ	•	+	•	•	-	+	+	+	+	+	•	+	•	•
T2	+	=		-	•	ϕ	-	-	+	ϕ	ϕ	ϕ	+	+	+	ϕ	-	+	+	+	+	+	•	+	•	+
T3	+	+	=	-	-	ϕ	-	•	+	-	ϕ	ϕ	+	+	+	•	-	+	+	+	+	+	•	•	•	+
T4	+	+	+	=		+	+	+	+	+	ϕ	ϕ	+	+	+	+	+	•	+	+ or -	+ or -	+ or -	•	+ or -	+	+
T5	+	•	+		=	ϕ		-	+	-	ϕ	ϕ	+	+	+	+	+	+	+	+	+	+	•	+	+	+
T6	ϕ	ϕ	ϕ	+	ϕ	=	ϕ	ϕ	ϕ	ϕ	ϕ	ϕ	ϕ	ϕ	ϕ	ϕ	ϕ	ϕ		ϕ	ϕ	ϕ	ϕ	ϕ	ϕ	ϕ
T7	+	+	+	+	+	ϕ	=	ϕ	+	+	ϕ	ϕ	+	+	+	+	+	•	+	+ or -	+ or -	+ or -	ϕ	•	+	+
T8	+	+	•	+	+	ϕ	•	=	+	+	-	+	+	+	•	ϕ	ϕ	+	ϕ	+	+	ϕ	ϕ	ϕ	ϕ	ϕ
T9	+	+	•	+	+	ϕ	+	ϕ	=	+	ϕ	ϕ	ϕ	ϕ	+	+	ϕ	•	+	+	+	+	ϕ	+	•	+
T10	-	ϕ	-	-	•	ϕ	-	- or +	+	=		ϕ	ϕ	ϕ	•	ϕ	ϕ	ϕ	ϕ	ϕ	ϕ	ϕ	ϕ	ϕ	ϕ	ϕ
T11	+	•	•	+	•	ϕ	+	ϕ	ϕ	•	=	ϕ	ϕ	ϕ	•	ϕ	ϕ	ϕ	ϕ	ϕ	ϕ	ϕ	ϕ	ϕ	ϕ	ϕ
T12	ϕ	ϕ	ϕ	ϕ	ϕ	ϕ	ϕ	+	ϕ	ϕ	ϕ	=	ϕ	ϕ	ϕ	+	ϕ	ϕ	ϕ	ϕ	ϕ	ϕ	ϕ	ϕ	ϕ	+
T13	•	+	+	-	-	ϕ	-	-	ϕ	ϕ	ϕ	ϕ	=	+	+	ϕ	-	+	+	+	+	+	+	+	+	+
T14	+	+	+	-	-	ϕ	-	-	ϕ	ϕ	ϕ	ϕ	+	=	+	ϕ	-	+	+	+	+	+	+	+	+	+
T15	•	+	+	-	-	ϕ	-	-	ϕ	ϕ	ϕ	ϕ	+	+	=	ϕ	-	+	+	+	+	+	+	+	+	+
T16	•	ϕ	•	+	+	ϕ	+	-	+	ϕ	ϕ	+	+	+	+	=	-	+	+	+	+	-	•	+	•	+
T17	+	+	+	+	+	ϕ	+	+	ϕ	ϕ	ϕ	ϕ	+	+	+	ϕ	=	+	+	+	+	+	-	-	+	+
T18	+	+	+	+	-	ϕ	+	-	+	ϕ	ϕ	ϕ	+	+	+	ϕ	-	+	+	+	+	+	+	+	+	+
T19	+	+	+	+	-	ϕ	+	-	+	ϕ	ϕ	ϕ	+	+	+	+	-	+	=	+	+	+	+	+	+	+
T20	+	+	+	+	-	ϕ	+	-	+	ϕ	ϕ	ϕ	+	+	+	ϕ	-	+	+	=	+	+	+	+	+	+
T21	+	+	+	+	-	ϕ	+	-	+	ϕ	ϕ	ϕ	+	+	+	ϕ	-	+	+	+	=	+	+	+	+	+
T22	+	+	+	+	-	ϕ	+	-	+	ϕ	ϕ	ϕ	+	+	+	ϕ	-	+	+	+	+	=	+	+	+	+
T23	•	•	+	+	-	ϕ	+	-	+	ϕ	ϕ	ϕ	+	+	+	+	-	+	+	+	+	+	=	+	+	+
T24	+	+	+	•	-	ϕ	+	-	+	ϕ	ϕ	•	+	+	+	+	-	+	+	+	+	+	+	=	+	+
T25	•	+	+	•	•	ϕ	-	-	ϕ	ϕ	ϕ	ϕ	+	+	+	•	-	+	+	+	+	+	+	+	=	+
T26	•	+	+	-	-	ϕ	+	-	+	ϕ	ϕ	•	+	+	+	+	-	+	+	+	+	+	+	+	+	=

ϕ	trend x has no identifiable impact on trend y
+	trend x leads to or is +vely aligned with trend y
=	Trend X: interrelation with itself
-	trend x is correlated with the reverse of trend y
•	Can't be determined currently

Table 9 Interrelationships amongst trends

Answer to Research Question 3: What is a Personalized Medicine Strategy? How can Personalized Medicine be commercialized?

A Personalized Medicine Strategy is a multi-pronged strategy that enables patients to access a combination of tailor-made drugs and treatment options. One prong of the Personalized medicine strategy deals with technologically enabling pharmaceutical and biotechnology companies to come up with novel drugs for each distinctly identified patient group. This can only be done if the regulatory concerns regarding new drugs, the innovation risks are well accounted for. The second prong of a personalized medicine strategy deals with identifying incentivization mechanisms which can be agreed by all major stakeholders, namely the developers, regulator, payers and dispensers. The third and the final prong of the personalized medicine strategy is enabling market access. This prong ensures regulatory compliances and lower drug costs, operationalizes healthcare institutions to administer personalized medicine appropriately etc. so that it can be beneficial to the masses.

To commercialize Personalized medicine successfully, apart from advances in the developing the therapeutics, it requires a unification of stakeholders across the pharmaceutical value chain and an enabling policy/governance environment. The success of a personalized medicine strategy will be determined by its translation into active day to day healthcare practices. Various approaches to personalization include health tracking mechanisms, advanced diagnostics for early disease detection and genetic profiling of individuals. With the use of DNA sequencing technologies, predictive modeling, study of proteomics and human phenotypes etc. researchers have been able to identify many root causes of diseases which were previously unknown. However, this basic research still has not been translated into a robust business model targeting the masses. Oncology has been the forefront of developments in Personalized medicine. While, there has been a huge success in commercializing and profiling individuals for certain types of cancer, the progress has not been extrapolated to other therapeutic areas currently. But on the bright side, the biomarkers and diagnostics industries are booming currently. However, experts uniformly share a concern behind the economics behind developing individual diagnostic tests and biomarker identification for a very small sub-strata of the affected population. To go through clinical trials for each new test becomes financially unsustainable especially when there is a huge doubt about payer re-imbursements once the novel diagnostic is launched. To add more complexity to the problem, to get to common ground with payers is yet not simple since it is difficult to establish by mutual consensus, the total costs saved by taking a diagnostic test as against not taking that test since the real outcomes would only be seen after months or years in some cases.

Answer to the Main Research Question: To what extent does a Personalized Medicine Strategy fit in with the new trends and disruptions in the Pharmaceutical Industry?

To sum it all up, Personalized Medicine is still largely limited to the areas such as cancer treatment and a sudden expansion of personalized medicine to other therapeutic areas in the coming 5-10 years remains less likely. However, the need for novel cardiovascular and immunological drugs has garnered attention. But expert opinions suggest that it would still be considered too ambitious for a pharmaceutical company to invest in developing personalized cardiovascular drugs because of a lack of specific predictive models. Most genetic interactions can now be modeled, as is done while developing oncological drugs, but many cardiovascular diseases are also dependent on lifestyle patterns which require in depth studies. Hence, the skepticism regarding personalized cardiovascular drugs in the near future. As far as the blockbusters are concerned, approaching patent cliffs are causing pharmaceutical companies to look for alternatives. The payers have become more critical about the type of medicines that they reimburse. These factors nudge the many traditional pharmaceutical companies to develop novel medicines which can be used to showcase product differentiation. Establishment of clinical data repositories and industry – research organization consortiums to accelerate drug development further signal a push in the direction of personalized medicine.

In the backdrop of these disruptions in traditional medicine, it must be noted that the enabling environment for personalized medicine – i.e. maintaining patient repositories, electronic health records etc. has progressed at a much slower rate. Healthcare centers have not been able to cope up with designing and installing systems that allow the use and transmission of electronic health data. Regulatory protocols concerning novel diagnostic tests and personalized drugs are also constantly changing as and when new scientific evidence is revealed. However, on the brighter side, innovative methods incorporating evidence from biomarkers are increasingly used design clinical trials This has a direct impact on the cost of development of a drug. Narrowing down targets right during drug discovery narrows down the number of compounds to be investigated. On the backend, to capitalize in such a scenario, a more collaborative approach is recommended. Integrating with med-tech, involvement of patients in the decision-making process are the starting points. Localized collection of patient data and translating it into clinically relevant data could foster the development of personalized medicine. A strategy focused on diversifying financial and project risks can help stimulate widespread adoption of personalized medicines. On the front end, industry and regulators should work in a consultative process. Until and unless, a regime shift across most pharmaceutical industries from the sales-based approach to a health outcomes-based approach doesn't take place, personalized medicine will only remain a niche offering. As for the current scenario, the market access to personalized treatments is very limited to the bulk of the population and this is unlikely to change in the coming 5-10 years or so. However, in the coming decades, we might witness a Personalized Medicine revolution.

Future Research Implications

In this section, interesting avenues to build on this research will be highlighted. In this study, the potential for personalized medicine to grow on a mass level was assessed. The contribution of this study to state-of-the-art literature is that the potential of personalized medicine is now assessed in the context of trends and their interrelationships from a multi-stakeholder point of view. Such a study was not done before. It was observed that changes in the regulatory framework must be in sync with the developments in technology as new kinds of clinical data become available. It was also observed that the factor limiting radical changes in existing business models is the high financial risk associated with following personalized medicine-based approaches. These observations point towards a need to develop mechanisms that can allow companies to collaborate and experiment with developing radically different drugs, which they otherwise wouldn't delve into due to huge financial requirements. This need can be satisfied by pathways that allow different organizations to either secure their research dedicated assets specifically for new drug developments or enter into mutually beneficial agreements. We identify that the ability to allocate assets for groundbreaking biotech/pharmaceutical research and multi-party collaborative arrangements are crucial for the success of the pharmaceutical-biotech and healthcare sectors since they are so heavily dependent on each other. Two promising pathways to investigate for future research emerge as a result of conducting this thesis.

1) Securitization and Portfolio Management
2) Risk Sharing Agreements

Insights on Risk Management

1) Focus on financializing the development of novel treatments for serious medical conditions – Via Securitization and Portfolio Management

In pharmaceutical and health sciences literature, there exists is a strong correlation between exponentially rising costs of drug development and unusually long product development cycles with regulatory uncertainties and shortage of liquid funds to pursue late stage development of multiple promising drug candidates.

There have been multiple cases spanning across the big pharma as well as small bio-technology firms where research had to be abandoned because the rates of returns on investments for the foreseeable future were extremely low and either due to the non-availability of funds, increase in the project risks above the maximum threshold value or due to estimated unfavorable market environments for drug commercialization.

This complete abandoning of advanced stage researches has an extremely bad implication on the masses in terms of a smaller number of revolutionary drugs and cures being approved per unit cost of R&D. As a result, in the grand scheme of things, there have been many diseases for which no complete cures are available. It could be reasoned that the underlying biological complexity of the disease is primarily responsible for not having cures for such diseases. Yet another reason cited is lack of continuous access to healthcare (especially in the developing countries). However, a major factor as to why there is a

shortage of research on identifying those bio-chemical mechanisms is the economic unattractiveness or simply put the lack of funding. Large data-sets of human and animal studies are required to be processed and experimenting novel combinations of treatments and monitoring mechanisms increase the research costs exponentially.

Take the example of Alzheimer's disease. Till date, there have been more than 100 drug failures to cure it. Even the top big Pharma companies such as Johnson & Johnson, Eli Lilly, Astra Zeneca have dropped pursuing novel drugs for Alzheimer's due to dissatisfactory results in clinical trials (Miller, 2019). Till date, despite having the most sophisticated technologies only treatments targeting the elimination of symptoms exist for the disease, none of which is actually focused on prevention or complete termination of the disease itself (Yiannopoulou & Papageorgiou, 2013). While companies such as Biogen and Eisai which are still developing disease modifying amyloid based treatments are losing stock value and investor support despite demonstrating a substantial progress in the research outcomes (Miller, 2019).

Despite the pharmaceutical industry's increasing focus towards developing novel drugs and treatments to cure rare diseases, a sizeable fraction of the population suffers from chronic diseases and medical conditions with no permanent cure. Some of the other examples are retinitis pigmentosa (an irreversible eye disorder), Schizophrenia (mental disorder affecting more than 21 million people globally) (World Health Organization, 2018).

While government organizations all across the globe have taken initiatives to interconnect and share data to expedite the developments of treatments for such diseases, the lacking impetus can be provided with the emergence of a network of diagnostic companies, bio-medical health providers as well as biotech companies to expedite R&D in disease areas which are almost considered as dead investments by current market standards. Yet another point raised in literature and also by one of the expert interviewees was the need to have a reversed model of the current translational research. Here, inputs are transferred by the physicians and patients to the laboratory R&D by observing the difficulties faced by patients (such as instabilities in cognitive and physical abilities) in their day to day life. This could help create a two-sided approach to tackling chronic diseases.

Incorporating business models with proven financial incentives and a demonstrably lower return of investment risk will be two decisive for private players to join forces and enter the risky territory of drug development in these life-threatening disease areas. A new type of funding mechanism called the 'mega-fund' is being developed by using the concept rooted in financial engineering called 'Securitization'. The current source of research and development funding in the mainstream pharmaceutical industry either works through venture capitalist funds, or financing via issuing public or private equity (Lo & Naraharisetti, 2013).

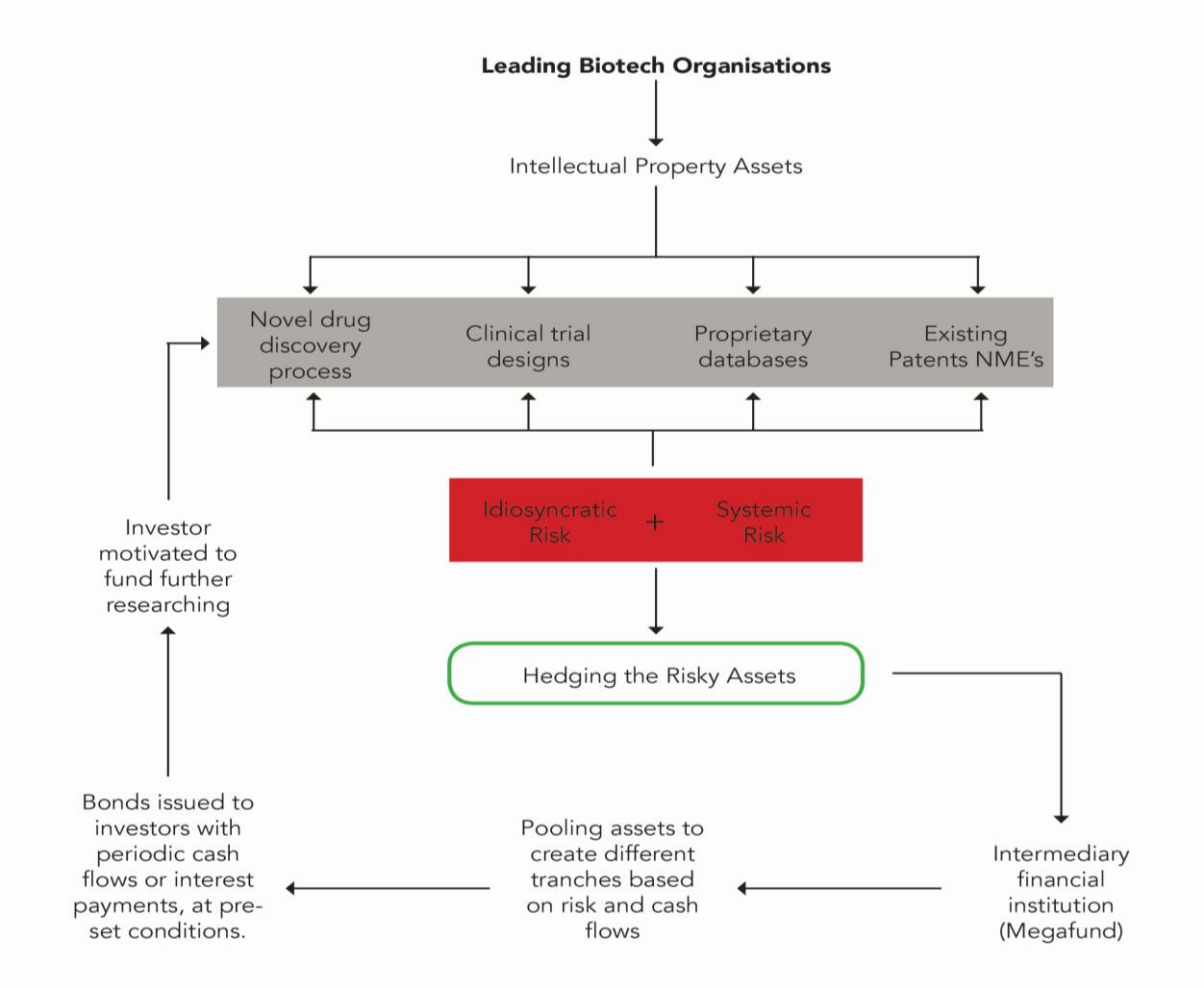

Figure 13 The Securitization of Biotech-Pharmaceutical Projects

However, debt financing has a much lesser cost of capital and a much larger market size. The reason why the cost of capital for debt financing is lower than compared to equity-based financing is that usually firms are required by law to fulfil debt obligations first and then, the earnings can be distributed to the equity investors. This means that there is less risk to a debt financing investor and hence the lower cost of borrowing. Yet another reason why debt financing could be particularly advantageous over equity financing is the fact that it allows to custom-spread the interest payments according to the needs of investors.

The idea is based on categorizing different pharma and biotech projects into different tranches based on three factors:

1) maturities of the projects (how long will it take for the project to complete?)

2)the associated probability of success of each project of a tranche

3) the estimated commercial value that the project may yield once the project is successful etc.

A tranche comprises of different financial securities (in this case - bio-pharmaceutical projects) ordered by the credit ratings based on the risks that each project carries.

Then a portfolio mix of these projects is customized and sold to an investor as a bond in exchange for guaranteed cash flows. This allows risk to be spread across the portfolio and the investor doesn't have to worry about the returns if some of the projects fail. Applying such concepts of financial engineering would stimulate more players to abandon the traditional R&D for tried and tested drugs and move towards projects with relatively high risk (Fernandez, Stein, & Lo, 2012). It would be extremely interesting to simulate these models for innovative pharmaceutical-biotech projects aimed at developing a novel companion diagnostic or a biologic/biosimilar etc.

2) Focus on developing risk sharing agreements between healthcare - pharma - payers - patients specifically for personalized medicine.

As stated previously, there has been an increasing number of Risk Sharing Agreements seen between the pharmaceutical companies and the payers. The risk here has different implications for both the involved parties. Risk for the payers refers to the potential loss of total sales as a result of selling a new drug or a new version of the same drug rather than the established drugs which have become the market dominant standard. For the pharmaceutical companies, often, it happens that after years of refining the existing drug or creating new drugs, there is a chance that the expected sales of the drug is much lesser than anticipated. This could be due to unexpected increase in market competition or due to inadequate market access. Inadequate market access occurs because pharmaceutical companies are either not able to satisfy the regulatory requirements in certain countries or their products aren't permitted to be sold in some countries/geographic areas due to similar pre-existing products. (Adamski et al., 2010) define risk sharing schemes as "agreements concluded by payers and pharmaceutical companies to diminish the impact on payers' budgets for new and existing schemes brought about by uncertainty and/or the need to work within finite budgets".

Answer to the Question: What are the risk sharing mechanisms that can be used by the Pharmaceutical Industry to propel the adoption of Personalized Medicine?

Two different types of risk sharing mechanisms exist. (Adamski et al., 2010) broadly categorize risk sharing agreements into two major types as listed below:

- Financial Sharing Agreements – These are the agreements that typically have been existing between pharmaceutical companies, insurers and other public-private payers since many years now. These agreements take various forms depending upon the type of market and the governmental healthcare policies in different geographic regions. Typical financial sharing agreements are Price Volume Agreements and price capping schemes((Adamski et al., 2010);(Zhang, Zaric, & Huang, 2011)).

  Price Volume Agreements involve paybacks or rebates paid by the pharmaceutical/biotech companies to third party payers if the total sales of a product exceed a predetermined threshold value. Since, the sales success of the drug is unknown in the initial stages of market launch, that risk is taken by the payer

when they reimburse the drugs for the patients. If the drug sales go beyond a mutually agreed quantity, the manufacturing companies (pharma-biotech) reward the payers by giving them paybacks or rebates. This reward is for the risk that the payers undertook by supporting the reimbursement for the drug developed by the pharmaceutical-biotech companies. A potential drawback of the volume threshold that is determined by the manufacturers and the payers is that (Zaric, Zhang, & Mahjoub, 2013)

Price capping schemes are aimed at limiting the costs bore by the patients. Often, for patients having medical conditions which require repeated prescriptions of drugs or therapies, the costs are shared by payers and the patient populations. The payers usually reimburse the patients up to a fixed number of repeat prescriptions or a up to a fixed monetary amount. The expenses in addition to those reimbursed by the payer are paid by the patients themselves. This sharing of payments is known as co-pays. Price capping schemes involve manufacturing companies covering the drug expenses of patients up to a specific number of treatment cycles/prescriptions.
An alternative form of a price capping (via dose capping) scheme is exercised when the manufacturers take responsibility to cover the treatment expenses of patients if they need to take a drug for more than a stipulated time period. For example, if a patient 'P' is still not cured of a chronic disease 'X' despite taking a drug manufactured by company 'ABC' for 3 years, then 'ABC' will bear the responsibility to facilitate free access of drug 'X' as long as the patient 'P' is not cured or decides to stop taking drug 'X'. Another form of price capping could be that the manufacturers pay for the first few treatment cycles or drug prescriptions. In case the health problem still persists in the patient, the costs for the extra treatments are covered by the payers (Zaric et al., 2013).

Recently, there has been a huge shift from the financial sharing agreements to outcome-based agreements. The key reason for this shift is although the former establishes a mechanism to control costs, it often overlooks the improvements in public health as it is largely sales driven (Pouvourville, 2006). More sales of a drug don't necessarily mean that the desired level of public health outcomes has been achieved. It just means that that specific drug has the best possible mix of market access, supporting medical services, efficacy, pricing etc. to address the market needs at that point of time. This leads to a more complex system of risk sharing called Performance/Outcome based Agreements. However, they are not used business practice currently.

- Performance/Outcome Based Agreements – The words Performance Based Agreements and Outcome based agreements are often used alternatively in literature. These are agreements where the pharmaceutical companies offer price discounts for drugs or combinations of drugs if they do not produce the desired level of effect in the patient population. Usually, the agreement mandates a fixed price of a drug reimbursed by a payer until a specific drug performance parameter is

observed over a pre-determined patient population size. The performance parameter could be patient's observable health, number of units consumed for a patient to reach a specific measurable medical end-point, mortality etc. However, if the performance parameter is not achieved, then the pharmaceutical companies are supposed to pay a mutually agreed fraction of the reimbursements to the payers.

Such types of agreements allow higher reimbursements for drugs with more efficacy and vice versa. However, a significant problem associated with performance-based agreements is that, often, it becomes difficult to gauge the true impact that a drug or a combination of drug has brought in a patient within the pre-determined time frame. This is because drug interaction with the human body is an extremely complex process and depends upon many factors such as individual lifestyle, medical condition, drug access, efficacy etc. Often, to see the true evaluation of a drug takes years or months. It might also happen that, the drug performance as compared to that obtained during the clinical trials varies drastically as the drug is administered to different population type. This could happen because, some types of patient population might not be present in the clinical trial analysis of drug performance. However, as more and more diverse groups of people start taking the drug, it might reveal drug response patterns that previously might not have been studied during the clinical trials. However, for performance-based contracts, this becomes problematic only if the performance can't be evaluated accurately within the required time frame in which financial transactions between payers and the pharmaceutical company need to be executed. Furthermore, if the expected benefits of a drug are not achieved or are partially achieved, it might lead to discontinuation of that drug from the list of drugs eligible for reimbursements. This might sudden lack of market access and in turn this affects the patient population adversely. If for some reason, the small segment of patients who benefit from that particular drug still need access to that drug, the expenditure then is transferred to the patient's out of pocket costs rather than payers. Hence, in some cases, there might be no real decrease in overall healthcare expenditure which is contrary to what is desired by most governments today (Gonçalves , Santos, Silva, & Sousa, 2018)

But, on the bright side, such performance-based agreements might stimulate more research and development in areas having an unmet medical need. The reason behind this is that often, the regulations are much more relaxed for new research and development programs targeting areas such as Rare Diseases.
Some of the examples of 'relaxed regulations' referred to in the previous statement pertain to drug approvals for pharmaceutical companies despite:

1) lesser number of clinical trials or merging two separate phases of a clinical trial
2) Smaller sized clinical trials (Meaning that the number of patients over which a drug is tested is lesser than in the case of traditional drugs.

3) Lowering the statistical significance level needed to generalize the findings of clinical testing etc. (Meaning that even though there is relatively less probability (compared to conventional regulatory standards) that the new drug might work on a

patient sub-population - If the anticipated benefits of the new drug outweigh the possible risks, the new drugs are approved.
4) Regulatory authorities could exercise flexibility in drug approvals for rare diseases even in absence of standardized efficacy endpoints of a drug (since there is not much historic data available to compare) (Margolis, 2018)

Hence, there still remains a considerable risk that a developed drug/cure would bring about any significant improvement in patient health despite being approved by the regulatory authorities. Also, the drugs used to treat Rare Diseases are extremely expensive as compared to the mainstream drugs sold in the market. Having such performance-based contracts can incentivize companies to maximize reimbursements by improving drug efficacy, drug safety & effectiveness and strengthen their revenues. A potential drawback of outcomes based risk sharing pointed out by (Renwick, Brogan, & Mossialos, 2016) is that it often becomes problematic to determine the optimal level of rewards for a specific outcome/performance parameter achieved by the biotech-pharma companies. Determining this optimal level of rewards is vital to stimulate biotech-pharma companies to improve and innovate, but at the same time, lead to a decrease in the overall health expenditure goals set by governmental agencies. Also, pre-setting a maximum possible monetary payment based on drug performance could possibly lead to pharma-biotech companies to lose interest in pursuing a drug if the reward is not viewed as under-proportion with respect to the time and resources invested.

Lastly, it must be pointed out that risk sharing by performance or based on outcomes is extremely complex. Sometimes, even though a drug developed by the pharma-biotech companies is highly effective, its result on overall public health outcome is not commensurate to its effectiveness. This could be because the enabling healthcare infrastructure is not developed or the supporting medical services are not adequate etc. (Pouvourville, 2006).

The need of the aforementioned risk sharing agreements is likely to grow when companies try to commercialize Personalized Medicine. This is because Personalized Medicine inherently involves higher technological risk as well as the external risk of market acceptance aside from the high financial requirements to develop it. Here market acceptance directly depends on the ease with which personalized medicine replaces the dominant standard - which are the conventional drugs manufactured by the pharmaceutical companies. The more efficiently these risks are shared amongst partnering organizations, the faster the commercialization of personalized medicine will be possible. However, personalization is also likely to add multiple layers of complexity to the existing risk sharing mechanisms.

Consider a future scenario where a large number of people actually start using biomarker-based diagnostics and predictive analytics-based solutions to know their likelihood to suffer from that disease in the future. Now, there will be sections of the

populations who respond positively (high risk) to the test and a sizeable part of the population who show less to almost no likelihood of suffering from a particular medical condition/disease. Now, from a payer's perspective - reimbursing the expenses of such tests across the entire patient population only to identify the select few susceptible individuals might not be an attractive business proposition. Furthermore, different medical conditions and diseases will require unique diagnostic tests leading to an inflated payer expenditure. Additionally, it becomes extremely complicated to determine the monetary value of the true benefit that a complimentary diagnostic test would bring to an individual as opposed to when an individual would not take that diagnostic test. This is because taking such a test could signal a potential 'patient' to undertake medical assistance but prove to be of no tangible monetary value for a person who is a non-responder to the test. Hence, quantifying these outcomes in monetary values becomes challenging (Garrison & Towse, 2017).

On top of this, the risk sharing process is complicated by difficulty in estimating the real health outcomes. Often, health outcomes are determined based on surrogate end points rather than clinical end points. (Fleming & Powers, 2012) define clinical endpoints as "measures directly how a patient feels, functions or survives where 'functions' refers to patients' ability to perform activities in their daily lives". They go on to define surrogate endpoints as "outcome measures (which are) used as substitutes for a clinically meaningful endpoint." Now, the way it affects the risk sharing is as following can be illustrated with an example stated in the work of (Shabaruddin, Fleeman, & Payne, 2015). TPMT (Thiopurine methyltransferase) is an enzyme therapy used to treat immune disorders. If TPMT enzyme therapy doesn't produce the desired effect in an individual, it leads to a condition called neutropenia which has no direct effect on a patient's observed health meaning that it is not a clinical outcome. However, it makes people extremely vulnerable to different bacterial infections which then manifests itself into other directly measurable patient effects. Hence, due to absence of data on the exact relation between surrogate and clinical end-points, it becomes extremely difficult to attribute a value of the therapy or a diagnostic test (Shabaruddin et al., 2015)

Continuing with the payer's perspective in the future scenario - let's assume for conceptual understanding that the payer is able to assess accurately the true value of monetary savings per patient. The most important issue then which needs to be addressed is regarding the setting of optimal rewards for the pharmaceutical-biotech companies, the diagnostic test developers and the cut that payers keep for themselves. Since, the value of a standalone diagnostic test drastically increases when taken in combined with a pharmaceutical drug, and vice versa, it would become extremely interesting to see how payers would individually reward pharmaceutical companies and diagnostic test developers. Determining this optimum level of rewards warrants an independent financial modeling research specifically in the context of personalized medicine.

The Personalized Medicine System 2.0

With the onset of data integrated health practices globally and the increasing use of computational modelling for drug development, we envision that the new personalized medicine based **Pharmaceutical-Healthcare-MedTech-Regulator ecosystem** will be radically different. The most important change that appears likely is in the structure of interactions between different industries within the ecosystem.

Traditionally, this ecosystem has been extremely linear in nature with very few feedback points. One of the major feedback points for the traditional ecosystem is the drug safety monitoring mechanism post market approval. However, these feedback points are often viewed as a financial burden by some pharmaceutical companies as they do not perceive any additional value coming out of this information. As a result, most of the times, these feedbacks are merely carried out for evaluating the market competition or sales, rather than to actually identify the attributes (example – improved safety) of the product itself. For instance, according to the USFDA, the manufacturers are only required to notify the regulators if they observe any adverse drug reactions (ADR). However, there is no mandatory protocol that necessitates each pharmaceutical company to have a post market surveillance (Resnik, 2008). However, in the case of EMA, there is a much more centrally controlled feedback mechanism that makes it mandatory to monitor each marketing authorization holder to conduct post marketing surveillance. Additionally, the EMA also has a provision to monitor the suspected adverse reactions from drugs. These steps taken by the regulators are commendable considering the huge amount of human and financial resources that need to be invested. However, in the traditional framework, the post marketing surveillance is largely aimed at improving drug safety when the drug reaches the masses. The other major identifiable feedback point in the current ecosystem is through doctors. It must be noted that some large pharmaceutical companies are extremely proactive towards the opinions of physicians, surgeons or other health practitioners. However, most of the times, this process lacks a clear step by step translation of doctors' observations into drug development procedure. Also, one of the points mentioned as a side note by Expert 5 was the fact that many small or medium scale pharmaceutical companies don't actually approach doctors to learn about the drug effects post administration. Rather, their post marketing efforts are focused on identifying pathways to boost their own product sales or to get an estimate of what price ranges would be desirable to promote their product. While, these efforts are important for a company from a company perspective, the pharmaceutical companies often miss the larger picture here. This larger picture is presented by the Personalized Medicine System 2.0 in the subsequent paragraphs.

The structure of the Personalized Medicine System is very likely to be cyclic in nature. What we could see in the near future is a chain reversal with multiple feedback points guiding the drug development process. This is in stark contradiction to the traditional process of drug development where little feedback is provided after the drug has reached the market. We are likely to witness a greater number of treatments developed to target the core cause of the disease rather than just alleviating or removing the symptoms of the disease (Ginsburg & McCarthy, 2001). As more information about the human genome and the biomolecular basis of the diseases will be elucidated, companies specializing in

diagnostics together with the bio-pharmaceutical companies are likely push for approvals based on surrogate markers. Surrogate markers as defined in the works of (Katz, 2010) are "a laboratory measurement or physical sign that is used in therapeutic trials as a substitute for a clinically meaningful endpoint that is a direct measure of how a patient feels, functions, or survives and is expected to predict the effect of the therapy." Currently, approvals based solely on such markers is not possible since, the entire bio-chemical complexity of the human body is not understood and observed surrogate markers are often misleading (signs exuberated by the patient post treatment could be positive/desirable, however clinically there could be no improvement.). But in the future, when we have understood such correlations in depth, the entire regulatory approval process could undergo a regime shift where evidence based on surrogate biomarkers could actually be used as a core approval criterion and not just as a supplementary criterion for approvals. In order to transition to such a system, we envision close knit work processes between drug developers and the regulators.

Additionally, another point of feedback will be added to make the system more robust right from the drug development stage. This point of feedback is the incorporation of patient preferences. On a very small scale, large pharmaceutical companies have started to analyze relevant content from social media, conducted voluntary preference evaluation tests and tried to translate these stated preferences into product features. It must be noted that it is incredibly difficult to translate patient perceptions and preferences on how a drug treatment should be into a working drug product. The range of stated patient preferences is so huge that incorporating each patient's preferences into the drug development remains as a distant dream. In the near future, with the help of healthcare technology assessment groups (HTA) and regulators, for the common disease areas, the most important preferences observed across a common profile of patients is likely to be identified methodically. Subsequently, these preferences might be considered to develop a new drug. However, it remains to be seen in which therapeutic areas will attempts be made to incorporate these preferences and what exactly are the associated difficulties to do so on the mass level. However, there is tremendous scope for incorporating such preferences in the Med-Tech industry. The personalized medicine system as stated by Expert 2 (as a side note) would be heavily reliant on medical devices for continuous health data monitoring and transmission. The accessibility, comfort, ease of use, costs, risks and benefits of medical designs are likely to be quantified in the near future. Based on these values, approvals would be granted by the regulatory authorities. The incorporation of patient preferences as a basis of regulatory approval has already taken place in the US and the EU. This is likely to increase across all different types of medical devices (Marsh, 2016).

From a systems perspective, it would be interesting to draw a comparison from the automobile industry which went through a regime shift in the late 90's. Some of the mechanisms that drove this change were: 1) flexibility in supply chains; 2) possibilities to modify existing manufacturing assemblies to increase modularity and 3) producing many different automobile models and selling the model which comes closest to a customer's wants or preferences. Often, it was found that some sort of monetary incentive was given to customers who were not able to get a product exactly as per their preferences (Brabazon,

MacCarthy, Woodcock, & Hawkins, 2010). Coming back to the Personalized Medicine framework, it can be observed that the modularity is analogous to modern gene editing technologies such as CAR-T, or CRISPR which help design drugs specific to a person. But as we saw earlier, such techniques are nascent. Even, in the foreseeable future, they are not likely to be materialized for mass human consumption. The modification of the assembly lines (in the automobile industry) to make it modular in a way is analogous with biomarker-based drug developments (in the pharmaceutical industry). The biggest takeaway from this comparison lies in the third analogy. In the automobile industry - Just as monetary incentives offered to customers whose preferences were not fully met were crucial in sustaining the mass customization approach; similarly, in the Pharmaceutical industry – some sort of incentives either monetary or service based will be crucial to sustain the personalized medicine ecosystem. These incentives should not just be there for the end user (the patient) but also interdependent industries such as CRO's or healthcare centers etc. The incentives could be prolonged access to certain medical services or technologies or discounted offers for treatment etc. For the Personalized Medicine system 2.0, it is envisioned that medical data from health monitoring centers, medical devices, hospitals will eventually be shared on a deeply interconnected secure public network. To facilitate this, companies specializing in data analytics and information processing and storage are likely to form tie-ups with the government regulators. It could be the case in the future, that, a new business model emerges where med-tech companies, healthcare centers etc. collaboratively pay and enter into arrangements which enable sharing of extremely sensitive public health data anonymously. The incentive for each entity could be the high-quality data that they can use to improve their own organizational processes. These networks inherently reduce the individual risks of all involved entities. The pharmaceutical industry can then make use of these network arrangements to expedite new personalized drug developments. However, the only pitfall of such networks are unsolved data privacy issues that emerge with such extensive sharing. Nonetheless, parallelly, academic researchers and government are working to conceptualize anonymized data market places which would be central to the Personalized Medicine System 2.0. Such networks will also allow multiple feedbacks, not just during the drug development process, but also during manufacturing, and regulatory approval steps as well.

8. Reflection

In this chapter, a reflection of the entire research is done on two levels. On the first level, the methodology used in this research will be critically evaluated. The options of improvement during data collection and analysis will be described. On the second level, techno-managerial recommendations to the readers from the pharmaceutical industry are given based on the results of this research.

Level 1 - Research Methodology & Approach

This section gives the reader an idea of how the same research could be designed, if it was done for the second time. First, the problem with the sampling process is described. Next, the improvements in data collection and sampling are discussed. Then the study measures such as the research reliability, transferability etc. are reflected upon. Lastly, the

As far as the primary data collection method is considered, there was an extremely low level of response rates from experts belonging to some of the top pharmaceutical and biotech companies. It is safe to assume that this could primarily be due to extreme confidentiality adherence and non-disclosure policies issued by most major biotech and pharmaceutical companies. This meant that the sampling process used in this research was by default a non-probability sampling process where the sample elements (interviewees) have no fixed probability of getting selected for data collection purposes. In this research, definite criteria for expert selection were set in a purposive judgement-based sampling technique. This means that the top executives, company board members etc. can be considered as a high quality data source if they meet a list of pre-determined criteria (Sekaran & Bougie, 2016). A drawback of this method of sampling is that - Although the data obtained from these samples of experts could yield meaningful results, it may or may not be generalized to the entire industry with a high degree of reliability.

To alleviate this problem, an approach such as cross verification of perceptions and industry practices were undertaken. This means that, the views and opinions projected by one expert were presented to the others in the upcoming interviews. But in doing so, what was overlooked was the fact that each expert had a different role in the pharmaceutical-biotech value chain. This implies that, no cross verification of opinions and views was done on two or more experts holding the same position in the pharmaceutical-biotech value chain. Although, there are many overlaps in the roles played by the experts (since all experts were highly experienced and holding executive positions) - a significant amount of their core responsibilities in the organizations differed. This could adversely affect the generalizability of the results that are obtained post analysis. This problem was identified during the data collection stage, but due to unavailability of experts, it couldn't be rectified. This is one area that can be definitely be improved during the future researches.

Fortunately, barring a few important exceptions, there were not many contradictory viewpoints amongst the experts that were interviewed. In hindsight, had there been significant amount of contradictions, an iterative process of data collection process rather than a linear process would be more effective. The current research design for cross verification could have yielded even more insights if the Delphi technique was used.

- **Alternative Technique:** Delphi is used for forecasting and scenario planning. A panel of experts are selected and sent questionnaires. Each expert's responses are recorded. Then, the collection of all responses is processed by the moderator and sent to all the experts anonymously. The experts can then review the responses of other experts and the underlying reasons. Based on that information, the experts have the option to modify their viewpoints. Multiple rounds of back and forth communication with the experts often brings them to a consensus or a point of sheer disagreement. The data collection is then stopped. If no consensus or impasse results, it is up to the researcher's discretion to stop the data collection process. To execute Delphi is an extremely time-consuming process since, the iterations can't be started even if the inputs from one of the experts are missing. Hence, expert availability is crucial for the execution of this technique. Since Delphi incorporates anonymization, it allows to reduce social biases (pressure on the expert to be consistent with their initial views). However, the future scientist should be aware of the 'researcher induced bias' which may creep in subconsciously while processing the results from the experts and sending it to the experts for the next round of evaluation (Grime & Wright, 2016). Researcher bias basically takes place when the researcher only acknowledges the findings that were expected and doesn't give enough emphasis on contradictory findings or anomalies. Such situations should be consciously avoided during Delphi. Use of a qualitative analysis software such as Nvivo or Atlas Ti could help in pointing out these anomalies.

- Working independently from an academic setting, it was extremely hard to get access to experts working in the industry and willing to share insights. Hence, it is recommended that similar future researches for the pharmaceutical industry should be done in collaboration with a supporting company. This allows prolonged access to experts as well as gives high quality information (under confidentiality). The implications on the various research measures are described more in detail later in this section.

- **Reliability & Validity:** A good qualitative study design must ensure the validity, reliability of the instrument that is to be measured. "Reliability is a test of how consistently a measuring instrument measures whatever concept it is measuring (Sekaran & Bougie, 2016). The 'Test-Retest Reliability' and 'Internal Consistency' are the tests that can be used to measure the reliability of this study. The test-retest reliability can only be measured when the experts are asked the same questions again after a significant amount of time has passed. If there is a huge unexplained change in their opinions, the reliability of the study is low whereas small or no change in the answers indicate a higher reliability. However, this test wasn't carried out because of time constraints. Also, the 'definition of a significant amount of time' varies in different industrial settings. For the pharmaceutical industry, it takes many years to witness a tangible change in market and regulatory conditions given the long product development and commercialization cycles. Hence, it was safe to

assume that the expert viewpoints on most critical issues wouldn't have considerably changed during the phase from data collection to results. Next, the internal consistency of this study was found to be very high. The experts were asked multiple 'check questions' that helped verify the stances they had taken early on in the interviews. Even though new information in the form of literature findings, other experts' opinions were presented to each expert as the interview proceeded, no changes in opinion or viewpoint was observed during the interviews. Hence, it was concluded that the internal consistency of the experts' viewpoints was fairly high despite not applying quantitative methods such as calculating Cronbach's Alpha. For future studies, a quantitative element could be added to demonstrate high reliability by using such measures (Chant, Chiang, Jhangiani, & Price, 2015). The Validity is a test of how well an instrument that is developed measures the particular concept it is intended to measure" As for the validity of the collected data, the research design in field or lab experiments is often formulated in a manner which allows the results to be transferred to an external setting or generalized to an external context (Sekaran & Bougie, 2016). Owing to the specific nature of the Pharmaceutical Industry (differences in regulations/product development regimes etc. from the mainstream manufacturing industries) and especially the concept of Personalized Medicine - the 'research transferability' to other industrial settings is not expected to be uniformly high. But, industries such as healthcare, medical-device technologies (med-tech) who work in conjunction with the pharmaceutical and biotech industries can use the findings of this research as starting points in developing public healthcare frameworks or personalized devices respectively. It would also be interesting to conduct studies highlighting overlaps in the strategic frameworks of other highly regulated industries such as food & beverages with the Pharmaceutical industry – thus expanding the research transferability.

- **Reflection on the content of this study** - This study has aimed to enlist the trends as well as interrelations associated with the dynamics of the Pharmaceutical Industry. However, the subsequent more advanced research framework should attempt to quantify the degree of impacts be it in terms of finances, outcomes of public health, advances in innovation or degree of market access. It must be acknowledged that to do this, access to confidential company level information is essential, which usually, the companies are hesitant to provide to independent student researchers. An element that has been relatively under-represented in this thesis is the detailed study of how the rampant mergers & acquisition activities, divestitures prevalent in the pharmaceutical industry are affecting innovation activities and as a result the societal welfare in general. Yet again, the specific nature of mergers and acquisitions, the underlying reasons (whether purely done to increase market outreach or to expand the company product portfolio etc.) are not made public. Hence, working from an industry setting would help here as well. To further build on these results, a country-specific study of differences in regulations and business practices could prove immensely helpful. Despite not setting out with a sole goal of mapping the power dynamics amongst different actors and stakeholders, this research does lay

the groundwork on the possible approaches that could be taken to develop mutually beneficial and sustainable relationships amongst them. All in all, this research was a stimulating learning experience. Assessing different strategic alternatives from the perspective of one of the actors is a small but important step forward to demystifying the complex Biotech-Pharma-Healthcare-Medtech-Government cluster.

Limitations

The limitations of this research are listed here. The research does not analyze the changes in the regulatory/legal/policy framework required to facilitate these changes in the pharmaceutical industry. Analysis of financial and product portfolios, cost/revenue structures for Big Pharma is not a part of this research. Business Model Innovations and impacts in interdependent sectors (Healthcare, Pharmacy Unions, Insurances, Med-Tech etc.) are beyond the scope of this thesis. Incorporating these elements in future researches would surely increase the complexity of the research but also, give a holistic viewpoint.

Level 2: Recommendations to the readers in the Pharmaceutical Industry:

In this section, a brief set of recommendations to the readers from the pharmaceutical industry are given. The recommendations range from managing innovative products and services to setting up inter-organizational collaboration via research and manufacturing activities. Since, financial certainty of returns on an investment is rare in the pharmaceutical industry, the recommendations stated below are given considering the feasibility of implementing them in the near future (5-10 years).

- The first recommendation is made based on the results of the expert interviews regarding the need to switch from the blockbuster business model. All experts acknowledged that there is a huge untapped potential for companies to divert their attention towards therapeutic agents based on antibodies – biologics. Such a view is also reflected across various articles in literature. The reason supporting it is that biologics have a huge potential for personalization, meaning that newly developed biologics can be modified to only act on desired pathogenic targets within the human body. Furthermore, they can be administered in various doses, frequencies and modes of delivery into the human body as per the requirements of the patients. However, despite such promising attributes biologics, the recommendation to readers from the pharmaceutical companies is the following:
  Rather than giving up on the existing product lines in pursuit of biologics, only a part of the product line that is consistently under-performing in sales or the product that has reached market saturation should be identified. Next, if it is clearly identified that the drop in the sales/market share is persistent despite investing significant resources to improve marketing and promotional efforts, it is time to consider replacing that product with a new biologic. However, to develop a biologic is currently only possible by a select few innovators (big pharmaceutical companies) in conjunction with leading biotechnology companies due to extremely complex nature of biologics, high costs of development and approvals compared to traditional chemical drugs. This causes a high market price for biologics targeting serious

illnesses or disease areas. Also, the pharmaceutical companies need to consider the switching tendencies of healthcare practitioners before completely focusing on biologics. The meaning of Switching tendencies is explained here – In order to achieve annual healthcare expenditure goals and decrease patient's costs, the healthcare practitioners initially recommend an innovator drug (for example, a biologic) and then slowly as the treatment proceeds, move towards a generic version of the innovator drug (in this example – a biosimilar) depending on its availability. Hence, the forecast of revenues and expenditures should account for such effects before finalizing an R&D strategy. In a nutshell, for a traditional pharmaceutical company, a straight jump to a completely biologics-based R&D is not recommended. Rather, a phase by phase elimination of under-performing drugs and replacing them by investments in biologics is a much more sustainable way to transition. For those companies with comparatively lesser resources than the innovators, a huge opportunity has opened in the form of biosimilars. But this still doesn't mean that all companies would be able to achieve short term financial gains and market dominance by simply switching over to biosimilars. This is again due to the complexities in manufacturing for biosimilars. Because biosimilars are derived from living cells and tissues with varying structures and biochemical compositions, it often occurs that replicating the exact same manufacturing process does not yield the same drug product. There are batch to batch variations which are not accepted by the regulatory authorities. To get a manufacturing license for biologics requires a high level of expertise and dedicated facilities – which require a lot of money. But on the flip side, the USFDA has developed regulatory pathways that give abbreviated approvals in the U.S. for biosimilars (Christl, n.d.). Abbreviated approvals mean that the pharmaceutical companies are exempted from conducting studies showing therapeutic benefits (example – exemption from some phases of clinical trials) since it has already been established previously. If the biosimilars can show comparative efficacy, and a matching toxicity profile with an innovator-developed reference drug, they can be approved (Isaacs et al., 2017). A distinct piece of advice of one of our expert interviewees also stated that many side-effects of long-term exposures to biosimilars and biologics might take 20-30 years to manifest as observable side-effects in patients. Hence, unless extensive studies are performed, over-reliance on biosimilars should not be established as the market standard. Other than that, until now, in general, investments in biosimilars have found to be very promising with the EMA showing the highest biosimilar approvals in the world (European Medicines Agency, 2017). So, the strategic recommendation for companies with slightly lesser resources than the innovators is to quickly capitalize on biosimilars even though it might require massive reorganization of their existing product lines. The reason why a quick move is recommended rather than a slow transition as in the case of biosimilars is because, given the favorable there is a probability that the market can get saturated with biosimilars in the coming 10-15 years. These fast-acting companies should first invest resources to establish standardized manufacturing processes that would in turn help them achieve market dominance 10-15 years down the line.

- A point of consensus amongst experts and the literature study was that the influence of patient (end-user) preferences is gradually, but surely, driving a change in the consumption patterns of pharmaceutical products in the recent years. This is because of the shift in the power dynamics amongst stakeholders. The patients now have access to medical monitoring services, medication kits and devices besides advice from healthcare care groups. Hence, from the perspective of pharmaceutical companies, targeting patients directly has become more complex since each offering made by the company is more likely to be critically evaluated by the patient community and healthcare groups. So, it becomes important to incorporate their opinion and perceptions into the innovation framework of the pharmaceutical industry. Instead of relying only on high drug efficacy to appeal to patients, in the near future, the competitive advantage for a pharmaceutical company is likely to be determined by:

  The quality of offering consisting of both - 1) a high drug performance vs costs ratio and 2) access to medical service (individual healthcare advice/ personalized treatment plans for patients, routine health check-ups, rebates in return for customer loyalty etc.) In order to do so, SERVQUAL or SERVPERF based healthcare research models can be used. These models identify the differences in public perceptions of healthcare service quality and performance versus the expected qualities & performances. There is a high chance that pharmaceutical companies would have to outsource these research-intensive tasks to external organizations since such researches are often not their core capabilities. There is also a high probability that the pharmaceutical companies start seeing this only as an added expenditure with no tangible value creation mechanism. To those companies, the added value of conducting such studies must be communicated. If designed aptly, these studies could potentially allow pharmaceutical companies to study the effects of multiple parameters affecting service/performance such as - quality of treatment offered (correlating it to drug efficacy), access to novel medicines, monitoring programs, effectiveness of personalized diagnostic tests, Availability of doctors, healthcare personnel etc. The outcome of such studies could be used to identify the avenues on which pharmaceutical companies can capitalize. There is already scientific evidence published recently in the works of (Shafei, Walburg, & Taher, 2019). The research contains multiple case studies where SERVQUAL or SERVPERF were used in public-private hospitals, critical care institutions. Changes made based on the outcome of those studies improved patient relations with the healthcare organizations and led to patient loyalty in some cases – which means that the patient chose to go to the same healthcare organization again. For the pharmaceutical companies, this indicates a very high chance of a positive return to investment in terms of customer loyalty or a sustained rise in sales of products and services. Hence, despite the short-term expenditure, pharmaceutical companies must consider conducting such studies and use the information to develop a more lucrative customer value proposition.

- For the success of personalized medicine, it is vital that pharmaceutical companies start to recognize the importance of long-term relative pricing. This means that the absolute price per unit of drug sold may be higher, but due to high performance, the total treatment duration, costs and dosages of drugs required is lesser than the other existing products. Such pricing mechanisms can work well in areas where repeated treatments are desired such as chronic diseases. It might be true that some payers might be reluctant to reimburse expensive drugs since that would mean higher short-term costs for the them. In such cases, pharmaceutical companies should remodel their launch campaigns to effectively convey the long-term benefits to patients and payers.
- Big pharmaceutical companies should consider the portfolio securitization approach in order to develop and commercialize drugs for areas with unmet medical needs. This reduces the financial risk despite one or more product failures during drug discovery and development. Furthermore, incorporating economic benchmarks during the drug development phase itself can also help. Pharmaceutical companies should also consider making early investments to understand lifestyle induced chronic diseases better. Since a sizeable population suffers from such lifestyle induced diseases, early detection and treatment has a huge market potential. Pharmaceutical companies, biotech and diagnostics must collaborate to extract business value in such cases. The focus can then be on preventive care by.
- Pharmaceutical companies should attempt to be even more open to cross-organizational research collaborations despite their concerns of technology spill overs.
- From a strategic perspective, the readers from the pharmaceutical industry should amalgamate two different approaches: The first is the reduction in costs of clinical trials which directly translates into a lower cost of finished drug product. This can be done by investing in pharmacogenetic or pharmacokinetic or biomarker studies. A challenge associated with biomarker studies is the fact that the upper and the lower boundaries of responses categorized as effective or usable need to be clearly defined. However, in reality, these boundaries are often not distinct. Because of this, the biomarker test could show a positive response for a patient who is actually not responding or vice versa. Such errors could directly affect the reputation of the new developed biomarker and in a chain effect, the sales of these biomarkers go down. The cascading effect further amplifies when the value of a drug associated with that particular failed biomarker is diminished (S. Kulkarni & Ma, 2013). These processes warrant huge time and dedicated efforts. The investments required to perfect many such processes throughout drug discovery and development may trigger opposition from the top management on the grounds of extremely high short-term costs with no certain outcome. A strong collaboration with academia is crucial to address such issues. This was also strongly recommended by experts 3 & 4 during the interviews. While it must be acknowledged that the resistance to invest heavily in such studies is valid, the long-term financial gain that could emerge through the subsequent network effects is massively underestimated. It means that, if separate public databases consisting of results from such studies are merged, the pharmaceutical

companies can identify targets accurately. They can have access to more clinical data and ensure thorough randomization during future clinical trials thus drastically reducing future drug development costs. The second approach is recommended directly by taking the suggestion of expert 1. The approach involves aligning the product portfolio in such a way that different personalized treatments and diagnostic tests are bundled to make the offering financially viable for public (government) and private payers.

- Lastly, the big pharmaceutical companies should not be afraid of divesting its secondary or tertiary capabilities and infrastructure. Rather than vertically expanding across the value chain, a broader lateral expansion via partnering is recommended. On a personal note, to make Personalized Medicine system 2.0 the reality, the pharmaceutical companies should consider taking the moral high ground and forego excessive profits for the sake of reduced healthcare expenditures thus enabling mass market access.

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10. Appendix

List of Questions asked to the interviewers

Attached below is the list of questions asked to the interviewees. Please note that the order of questions may have been modified at the spot based on the responses given by the experts. Confirmatory questions and findings from previous interviewees were also asked spontaneously to validate findings, identify points of consensus between the experts. Specific overlaps between questions asked to different experts were designed such that clear difference of opinions can be pointed out in the analysis.

Before, conducting the interviews, the experts were sent a one-page email that includes the introduction to the thesis topic. Along with the thesis introduction a short summary of interest areas was mentioned. The experts were then asked to elucidate the trends that they think are the most in the context of the interest areas important and subsequently the inter-relations were mapped out.

Side Note: Since all the experts rightly found my first question (i.e. identifying the most important trends) very broad, they were provided a list of interest areas prior to the interview session.

Primary Questions answering the Research Questions.

1) What are the main trends that you see in the pharmaceutical industry today?
2) Do you see any interrelations between these trends? For instance, emergence of one of the trends you mentioned directly affects the emergence/obliteration of the other trends? If yes, could you provide me with some examples?
3) My focus area in the list of trends is Personalized Medicine. I would like to know your views on its techno-commercial feasibility and perhaps some regulatory aspects pertaining to it.
4) Could you briefly highlight the most important trends and strategies that pharmaceutical companies should focus on? (If possible, on a 10-point scale) And a one liner reason why?

Prepared Pool of general Follow Up Questions based on the different topics that the answers might cover:

- Regarding Healthcare Costs:

If healthcare costs are rising, which area/s of the pharma value chain do they think must be improved?

Example: Which areas need most attention? R&D streamlining, or a regime change in the manufacturing sector? Or does it have more to do with the stringent government regulations?

- Regarding Business Models

Why do you think most pharmaceutical companies (the bigger ones) are shifting from a blockbuster business model to a more robust business model (basically a lean business model)

My research suggests patent cliffs are a major factor (sales being eaten by generics)

Example (for the researcher's reference) Abbott split into two parts [an innovative business (AbbVie) and a diversified healthcare company (Abbott)]; GSK and Novartis swapped their oncology, consumer health and vaccines business to create focused organizations with GSK increasing the focus on consumer health and vaccines and Novartis on oncology; AstraZeneca narrowed the focus to three core therapy areas of oncology, cardiovascular metabolism and respiratory, inflammation and autoimmune disease, and in the process divested infectious disease and created a semiautonomous, virtual unit for neuroscience; and Bristol Myers-Squibb

- Regarding the Drug Development Process:

What sort of economic benchmarks do you associate with the R&D process? How do you determine a portfolio that the company?

Recently, according to my research, many companies have started to use portfolio management and even option pricing of

Do you see any threats/opportunities to improvise on the blockbuster business model?

One of the interrelations that I observed in my study as a result of the interrelation between rising healthcare costs and the need for enhancing the drug development process was the estimation of clinical and economic endpoints and then decide if its actually worth investing more resources to develop the drug further? Do you agree with this? Why/Why not?

Clinical trials constitute of the major costs of drug development and validation. What steps does the R&D departments big pharma companies take steps to control out of pocket costs of clinical trials? What are the barriers to it? What influences the choice of collaboration with external research organizations that specialize in clinical trials? Do such collaborations offer a significant advantage in terms of managing costs, expertise etc.

Side Note: You've been responsible for developing many synthetic drugs for the company. What are some of the biggest drawbacks of the way drugs are developed currently (drawbacks related to generics, synthetic routes of drug manufacturing?

- Regarding Collaborations:

There have been many initiatives taken by the governmental agencies in EU and the US to facilitate research across networks and expedite drug commercialization. For example – the European Federation of Pharmaceutical Industries and Associations which is a common network between Big Pharma companies and innovative SME's. In your opinion, does establishment of such organizations helping solve the drug commercialization problems. To what extent?

An unprecedented rise in Big Pharma's collaboration with academia, small scaled bio tech start-ups has been seen. Do you think it really is the answer to all the problems? Why/ Why not?
Do you think crowdsourcing and open innovation can actually be applicable to the pharma industry which currently creates significant competitive advantage through creating Intellectual Property and protecting it?

- Regarding Personalized Medicine

In order to develop and commercialize Personalized medicine, there are many technological barriers such as developing and validating biomarkers for detecting medical conditions, computational and bio-informatics limitations due to non-availability of required data etc.

For a traditional pharmaceutical company investing to develop personalized medicine, what is the approach that it should take in order to resolve these challenges. In other words, how to utilize the strengths of molecular profiling, genome sequencing to have a greater impact?

In your view, how should companies go about in solving the Innovator's Dilemma? (I.e. if you actually believe that there is a dilemma)
Side Note: Often, it has been noted that despite Personalized medicine showing great potential is not adopted by conservative pharma companies because of its existing investments in the current product lines. They suffer from the Innovator's Dilemma. How to go around that?

Many conservative big pharmaceutical companies are often not inclined to switch to personalized medicine because they don't see any threats to their blockbuster products despite patent cliffs. They continue to enjoy their market share due to either product monopoly, arrangements such as pay for delay deals, patent extensions etc. What is the strategic relevance for them to shift towards Personalized Medicine?

Do you see market uptake of personalized medicine being hampered by stakeholders down in the pharmaceutical value chain such as payers, pharmacy managers etc.
What economic effect do you think it will have on the payers and the end-user? In your opinion, will those factors be vital to determine its adoption? (Or – just the promise of a more effective cure will be enough to propel adoption.

Do you see some therapeutic areas performing much better when it comes to Personalized Medicine? Why do you think that is? Is it changing any time soon?

Extra Question: A lot of focus (off lately) has been on Rare Diseases. To what extent will Personalized Medicine be able to solve this problem?

- Regarding Contract Manufacturing

  Do you think CMO's are changing the existing manufacturing landscape of the pharma industry. Do you view outsourcing of non-core competencies as the way forward?

(According to literature, there are many knowledge spill-overs, differences in strategic visions that might hamper complete outsourcing. Do you agree with that?)

Do you see market uptake of personalized medicine being hampered by stakeholders down in the pharmaceutical value chain such as payers, pharmacy managers etc?

Specific Questions – Interview 1 (Expert 1)

1) Could you give an overview of some of the key responsibilities and the kind of decisions that you have to make at your position?

2) Do you see a changing landscape in the way Pharmaceutical Research and Development Strategies are made compared to 10 or 15 years ago?

3) (Follow up) How has that driven the pricing specifically in Europe?

4) (Follow up) What is your take on companies extending their product life cycles since you mentioned out of court settlements. Is that changing? If so, how?

5) Can you elaborate on the trend you mentioned about the market competition being driven by generics in the Pharmaceutical industry currently?

6) Do you believe that there is actually a strategic shift from the traditional pharmaceutical blockbuster business model to alternative models? Why/Why not?

7)How has the industry's strategic preference based on therapeutic areas evolved recently?

8) What is your take on biologics and biosimilars along with companion diagnostics emerging in the pharmaceutical industry?

9) Can you highlight how the portfolio selection of drugs for development and commercialization has changed? What kinds of models do most traditional companies use?

10) What sort of economic benchmarks are incorporated currently in the R&D process? Are go/No go decision gates used?

(Follow up) To what extent is option pricing incorporated?

11) Could you highlight some regulatory barriers that have emerged currently and why do you think so?

Specific Questions: Interview 2 (Expert 2)

1) Open Question – Could you give me a brief list of the most important trends that you see currently shaping the pharmaceutical sector?

2) With a steady improvement in diagnostics, molecular and gene sequencing, patient profiling techniques etc. personalized treatments are often predicted to rise in the future, meaning that people suffering from the same conditions might be given customized treatment/drugs based on the anticipation of how they will react to the drug. How do you see this changing landscape? Do you believe personalization for all treatments at a mass level is possible?

3) You have already developed models for digital health platforms and if I understand correctly, you strongly feel, it will slowly but surely change the way the current clinical practices/patient engagement etc. are carried out. Do you also feel that having personalized treatments for different patient sub-strata, the pharmaceutical companies need to re-model their existing business regimes?

4) An analysis of scientific Literature reveals that Personalized medicine while extremely efficient to cure specific diseases, doesn't have standard protocols which can be followed by doctors. As a result, treatments would still be done on the largely based on the subjective interpretations by the doctors. Do you see it as a hindrance for the adoption of Personalized Medicine?

5) Some experts say that Personalized medicine could slowly shift control from health professionals/medical personnel to patients and payers. There have been cases where the Formularies in the US and some major Pharmacies in Europe have been given discretionary powers to replace a drug that's not economically viable. Since you prescribe medications to people daily, do you think cost is a big issue as far as prescribing synthetic drugs is concerned? Do you think pharmaceutical companies should work on making drugs cost effective from the R&D phase itself?

6) Are there any clinical areas where personalized treatments are more urgently needed than the others? (For instance, researchers have to some extent been able to develop personalized cancer cures based on analysis of biomarkers present in the human body) Broadly speaking, which clinical areas have relatively satisfactory results from the currently available medicines (one-size fits all medicines)?

7) Traditional pharmaceutical companies are largely dependent for their product sales on their interaction with doctors, health practitioners etc. With the onset of personalized medicine, do you see this changing? If so, what would be an efficient manner from the pharmaceutical company's point of view?

8) What are the key factors that could expedite time to market for personalized medicine. Could you highlight a few Technological/ Regulatory difficulties in opting for a Personalized Medicine in place of a tried and tested synthetic drug that is the market dominant standard.

9) What kind of inter-relations do you see amongst these trends? If you were to rate the trends in the order of importance, how would you rate them?

10)All in all, to what extent do you think the world is going towards personalized medicine?

Specific Questions: Interview 3 (Expert 3 & Expert 4)

1) For starters could you describe a bit about the technology that you have developed and the basics about your business model?

2) Since my research is about identifying trends in the pharmaceutical industry, and accuracy in the drug discovery stage has directly been linked to higher commercialization potential. Could you enlist a few trends in how the drug discovery landscape has changed in the recent years?

3) (For interviewer's reference) Although identification of LPL (lipoprotein lipase) activating small molecules is eagerly awaited, screening of compound libraries is nowadays impossible, as it is extremely challenging to study LPL activity in an in vitro setting due to its complex

mode of action, which requires direct crosstalk between endothelial cells and metabolically active tissue.

Could you give some examples of how predictive analytics (access to information regarding genotypes and phenotypes) are expediting the process of drug development? In your experience, do you see any clinical areas where personalized treatments are more urgently needed than the others? High throughput screening cost metrics – is it affordable by small scale companies?

4) My research suggests that about 35% of the drugs globally in the R&D pipeline are for only one therapeutic area - oncology mainly because a lot of personalized treatments have started to come into the market (Eg -Herceptin). And relatively less importance has been given to important therapeutic areas such as cardiovascular, immunological drugs etc. Do you think this is true (generally speaking) Could you give some reasons as to why this might be the case? Does it have something to do with market saturation or simply because not enough research has been done on it?

5) Regarding biomarkers – There are various different types of biomarkers (protein biomarkers/imaging biomarkers) There are more than 200 biomarkers for lung cancer alone. But only 5or 10 are driver mutations. And I read that in many cases like these, companies often can't consensus amongst the scientific community. Do you think it's true for many new personalized medicines or only true for some special cases?

6) My next question is regarding a future trend. My research suggests that in therapeutic areas such as rheumatoid arthritis, about 50% of the people simply don't respond to drugs. So, diagnostic companies will try to identify such areas where there is a drug wastage and they should exponentially grow but they still won't since the current re-imbursement models don't support them extensively. Do you agree with this trend?

7) In your opinion, what barriers do you see in the development and adoption of Personalized Medicine? (Economic/Regulatory or more technological/barriers due to lack of data)

8) In the future, what sort of collaborations do you believe would help propel the adoption of Personalized medicine? Is PM something that all companies will aim for or will it exist simultaneously with the traditional medicines.

Specific Questions: Interview 4 (Expert 5)

1) Could you give an overview of some of the key responsibilities and the kind of decisions that you have to take as the International Marketing Manager of your organization?

2) Broadly speaking, could you think of some disruptions or let's say trends that are shaping the pharmaceutical industry? It could be Trends related to the business model, trends related to how internal/external R&D is conducted, product launch trends, market access trends etc.?

3) If you were to rate these trends in the order of importance, how would you rate these? May I know the rationale behind rating them so? (In other words which trends do you think are more important than the others and why?

4) Regarding Business Models - Example: Abbott split into two parts [an innovative business (AbbVie) and a diversified healthcare company (Abbott)]; GSK and Novartis swapped their oncology, consumer health and vaccines business to create focused organizations with GSK increasing the focus on consumer health and vaccines and Novartis on oncology; AstraZeneca narrowed the focus to three core therapy areas of oncology, cardiovascular metabolism and respiratory, inflammation and autoimmune disease, and in the process divested infectious disease and created a semiautonomous, virtual unit for neuroscience; According to my research , most pharmaceutical companies (the bigger ones) are shifting from a blockbuster business model to a more robust business model (basically a lean business model) Do you see this happening as a market wide phenomena or is it largely restricted to the top companies? Why/Why not?

5) Next, I want to raise the point about patent cliffs acting as the major factor (sales of the innovators being eaten by the influx of generics) Would you rate it as a trend that dictates substantially the behaviour of the pharmaceutical company or do you think it's something else that has caused pharmaceutical companies to seek competitive advantage like never before.

6) You have played a role in in-licensing products for your company. Could you highlight what factors do you consider before in-licensing a product or a technology? What would be of paramount importance for you to make that decision and why? Do you see this landscape of in-licensing changing in the near future (let's say the next 5-10 years)?

   For the researcher's reference - I ask this because, I read that there is an increasing strategic focus on biologics and rare diseases. Some examples are: Roche and Genentech for biologics in 2009 as well as Sanofi and Genzyme for rare diseases and biologics in 2011 are such cases, as are Pfizer' acquisition of Wyeth for biologics and

of Hospira for entering biosimilar business and AbbVie's acquisition of pharmacyclics for oncology business and to offset reliance on Humira1

7) According to a study conducted by the Tufts Center for the Study of Drug Development, "the life cycle costs incurred from developing a new prescription drug to gaining post-market approval is approximately $2.87 billion in 2013 which is 145% higher than in 2003 and this keeps on increasing. One of the explanations given is due to the proclivity of pharma companies to undertake riskier projects to gain competitive advantage." Now, from a company developing generics, do you think that these pressures significantly affect the way you price and market your products? Or do you think that it is pertinent to companies developing new drugs? (the rising healthcare costs/ government pressure to price the drugs as low as possible) (Dimasi, Grabowski, & Hansen, 2016)

8) Since you market drugs to so many different countries, do you identify a need to personalize medicine? For example – Herceptin for Breast Cancer (the treatment is customized based on patient profiling via diagnostics rather than completely. Do you see a therapeutic area with tremendous potential where personalization can do wonders in the coming few years?

9) What is your take on the techno-commercial feasibility of personalized medicine? Developing diagnostics, molecular/genetic profiling etc. as replacements for the conventional therapeutic drugs

10) My next question is regarding developing and commercializing Personalized Medicine Personalized medicine, there are many technological barriers such as developing and validating biomarkers for detecting medical conditions, computational and bio-informatics limitations due to non-availability of required data etc. For a traditional pharmaceutical company investing to develop personalized medicine, what could possibly be the approach that it should take in order to resolve these challenges.

11) According to a report by Bain and Company, "about 25% to 80% of the pharma industry's revenue would come from new launches by 2021 and at the moment 50% of launches over the past eight years have underperformed analyst expectations. More than 25% have failed to reach even 50% of external revenue forecasts". The reasons cited are the failure to convey their market research to payers and providers whilst only relying on the stage III clinical trials as a source of product differentiation (Natannek, Schlegel, Retterath, & Eliades, 2017) Do you agree with this? Why/Why not? They further state that conducting post-launch evidence plans can greatly help to change this situation, but is it worth the extra expense and efforts (in your opinion)? How feasible is it for medium scaled companies to do so?

As a follow up Question to that, would you consider getting to the market first as absolutely crucial in this scenario even though it means at the cost of getting a slightly inferior product than what you could have.

12) Lastly, do you see Personalized medicine as a replacement to the mainstream blockbusters or as something that will exist side by side along with it in the foreseeable future (5-10 years)?

Specific Questions: Interview 5 (Expert 6)

1) Could you give an overview of some of the key responsibilities and the kind of decisions that you have to make at your position?

2) Broadly speaking, could you think of some disruptions or let's say trends that are shaping the pharmaceutical industry? It could be Trends related to the business model, trends related to how internal/external R&D is conducted, product launch trends, market access trends etc

3) One of the trends that I came across was the exponential rise in biologics and biosimilars. Also, the research says that there is going to be a rise in companion diagnostics. Do you think, this is replacing the existing business model to produce blockbuster drugs. Or is it just a small niche alongside the mainstream business model? Why/ Why not?

4) My research suggests that about 35% of the drugs globally in the R&D pipeline are for only one therapeutic area - oncology mainly because a lot of personalized treatments have started to come into the market (Example - Herceptin). And relatively less importance has been given to important therapeutic areas such as cardiovascular, immunological drugs etc. Do you think this is true (generally speaking) Could you give some reasons as to why this might be the case? Does it have something to do with market saturation or simply because not enough research has been done on it?

5) Could you highlight a few trends as to how drug discovery is changing compared to what it was 10-15 years ago? (How genomics and proteomics have created new targets for drug discovery) Do you think, in general that companies need to work to reduce the cost of clinical trials or are their hands tied?

6) In your opinion, what barriers do you see in the development and adoption of Personalized Medicine in the near future? (Economic/Regulatory or more technological/barriers due to lack of data)

7) What sort of economic benchmarks do you think is suitable when working towards developing personalized treatments? Does using traditional (Internal rate of return or net present value do justice to these treatments?)

8) Some of the articles that I read says that biologics are soon going to take over synthetic drugs mainly due to the lesser side effects. But then, I also read that there are no clear guidelines especially in the U.S. as to how to regulate it.

For Researcher's reference - (The European Medicines Agency ("EMA") regulations do not require the applicant to obtain comprehensive data on patient benefit. The EMA requires the follow-on applicant demonstrate "similar efficacy and safety compared to the reference product.")