Strategic pharma/biotech R&D portfolio management: Analysis of internal and external project planning

Master Thesis
at Frankfurt School of Finance & Management

Supervised by

Prof. Dr. Jochen Schlapp
Prof. Dr. Horst Löchel

Submitted by
Stefanos Varntanian
Master of Business Administration
Full-Time MBA 2020
8416589

Frankfurt am Main, August 2020

Executive Summary

This research attempts to investigate how pharmaceutical companies manage their R&D portfolio in terms of internal and external project planning. Having a number of balanced projects that align with the company's strategy is complicated partially due to funding constraints and possibly also due to lack of specialised know-how or technological capabilities. Therefore, this study also focused on understanding the policy approach of pharmaceutical companies towards complementing their R&D weaknesses and achieving high-value portfolios in their main therapeutic areas. The project draws on provided proprietary data of six biopharmaceutical firms for the purpose of this thesis.

Data analysis in regard to clinical phases, mechanism of action, size of arrangement deals, asset and transaction types revealed certain patterns that all major firms follow. The evaluation showed that firms tend to utilize compounds with inhibit antagonist characteristics, because of their frequent use in major portfolios such as oncology and neurology. In addition, majority of the transaction deals took place during either the discovery, mainly for the licensing of technological platforms that could accelerate drug identification or the approved stage where business units or products were acquired in order to enhance portfolios that suffered setbacks.

Based on the findings from the data inspection, it is recommended that intelligence input from more pharmaceutical companies is required in order to fully comprehend the essence of R&D portfolio management and how detrimental is correct project planning for the prospective strategy of a firm. This will also provide better insight into whether there is an advantage in licensing deals rather than increasing investments into internal R&D and trying to strengthen in-house expertise in areas of interest.

List of Tables

Table 1: Overview of the drug development process. 12
Table 2: Size of transaction deals in relation to the stages in drug development. 18
Table 3: Primary asset types at each clinical stage. 19
Table 4: Size of transaction deals at each clinical stage. 25
Table 5: Preference of asset types during clinical stages. 25
Table 6: Size of transaction deals at each clinical stage. 31
Table 7: Main asset types during individual clinical stages. 32
Table 8: Size of transaction deals at different clinical stages. 37

Table 9: Preferred asset types of AZ during the clinical stages. 38
Table 10: Size of transaction deals completed by Roche. 44
Table 11: Preference of asset types at each clinical stage. 44
Table 12: Size of transaction deals at each clinical stage. 50
Table 13: Main asset types during individual clinical phases. 50

List of Figures

Figure 1: Key components of R&D productivity. 7
Figure 2: Assessment of anticipated commercial value of a project. [8] .....
9 Figure 3: Novo Nordisk's priorities regarding developing new drugs in certain therapeutic domains. .....
15
Figure 4: Main mechanisms of action of drugs produced by Novo Nordisk. .....
15
Figure 5: Primary technology used in drug discovery. .....
16
Figure 6: Transaction occasions during different stages of R&D development. 17
Figure 7: Size and number of transaction deals. 18
Figure 8: Classification of Novo Nordisk transactions. 19
Figure 9: Asset types used in transaction deals. .....
20
Figure 10: BI's involvement in a range of therapeutic domains. .....
21
Figure 11: Key mechanisms of action of medicines generated by BI. 22
Figure 12: Technology utilized by BI for drug discovery and development. .....
23
Figure 13: The occurrence of transaction deals during each clinical phase. 23
Figure 14: Size and Number of transaction deals. .....
24
Figure 15: Three main types of transaction undertaken by BI. 26

Figure 16: Frequent asset types used in transaction deals. 26
Figure 17: Takeda's main therapeutic areas. 27
Figure 18: Leading mechanisms of action of medicines generated by Takeda. 28
Figure 19: Different types of clinical technology used by Takeda. 29
Figure 20: Occurrence of transaction deals during different clinical phases. 30
Figure 21: Size and number of transaction deals of Takeda. 30
Figure 22: Types of different transactions undertaken by Takeda. 32
Figure 23: Types of different assets frequently preferred by Takeda. 33
Figure 24: Major therapeutic domains of AZ. 33
Figure 25: Main mechanism of actions of compounds. 34
Figure 26: AZ's preference of technology for drug discovery. 35
Figure 27: Frequency of transaction deals during each clinical stage. 36
Figure 28: Number and size of transaction deals involving AZ. 36
Figure 29: Different types of transaction undertaken by AZ. 38
Figure 30: Preferred asset types in transaction deals. 39
Figure 31: Core therapeutic areas of Roche. 40
Figure 32: Main mechanisms of action of medicines manufactured by Roche. 41
Figure 33: Primary technology used by Roche for drug discovery. 41
Figure 34: Frequency of transactions during the clinical stages. 42
Figure 35: Size and number of transaction deals by Roche. 43
Figure 36: Main types of transaction deals undertaken by Roche. 45
Figure 37: Frequent asset types used in transaction deals by Roche. 45
Figure 38: Major therapeutic areas of Merck. 46
Figure 39: Mechanism of action of medicines manufactured by Merck. 47
Figure 40: Various primary technologies utilized by Merck. 48
Figure 41: Frequency of transaction deals made by Merck at different clinical stages. 48
Figure 42: Size and number of transaction deals undertaken by Merck. 49
Figure 43: Different types of transactions undertaken by Merck. 51
Figure 44: Three main asset types during transactions deals. 51

Table of Contents

Table of Contents

Chapter 1 Pharmaceutical R&D Landscape 7

1.1 Problem Statement 7

1.2 Conceptual Framework 8

Chapter 2 Literature Review 9

2.1 Portfolio Management 9

2.2 R&D Portfolio Management 11

2.3 Pharmaceutical Portfolio Management ..... 11 2.3.1 Pharmaceutical Portfolio Management Techniques 13

Chapter 3 Methodology 14

3.1 Research Objective 14

3.2 Novo Nordisk 14

3.3 Boehringer Ingelheim 20

3.4 Takeda 27

3.5 AstraZeneca 33
3.6 Roche 39
3.7 Merck 45
Chapter 4 Licensing deals vs internal R&D 52
Chapter 5 Conclusion 53
REFERENCES 54

Chapter 1 Pharmaceutical R&D Landscape

1.1 Problem Statement

The pharmaceutical industry can be described as a high-fixed low-cost marginal cost industry. This is based on the fact that introducing a new drug to the market is not only a complicated issue, but also an expensive and risky process. It is more cost-effective to produce an extra unit of an already approved and on the market drug, which is often referred to 'pennies a pill'. **[1]**
One of the most important sectors of the pharmaceutical industry is research and development (R&D), which amounted to a worldwide spending of $141 billion in 2006, increased by 40% in 2015 and is projected to show a substantial growth of 60% in 2020. Following these numbers, it is reasonable that there are expectations for a high return on investment (ROI). However, the extremely low rate of introduction of new molecular entities (NMEs) and their commercialization do not correspond to the soaring R&D expenditures and in turn lead to failure of accomplishing growth objectives set by the industry. This puts the sustainability of the current R&D model in question and forces pharmaceutical companies to review the challenges they are facing as well as explore other growth options. **[2]** One key challenge is improving R&D productivity, which could possibly provide sufficient innovation to substitute revenue losses stemming from a variety of reasons such as patent expirations and high late-stage attrition rate during drug development. **[3]**
R&D productivity can be characterized as the relationship between the value an NME creates in terms of commercial and medical sales and the investments required to produce this entity. It is a two-dimensional parameter with inputs (R&D investments) leading to outputs (NMEs) and outputs leading to outcomes (value for patients). A schematic representation of the interpretation of the term R&D productivity can be seen in Figure 1. **[3]**

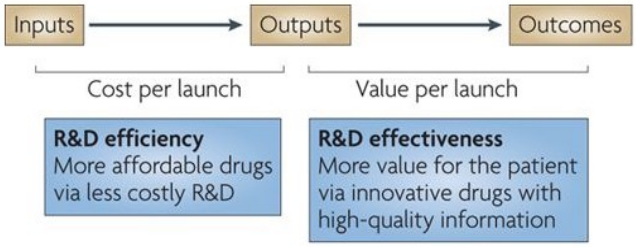

Figure 1: Key components of R&D productivity.

Although, R&D has experienced a surge in investment the last two decades, pharma productivity faces challenges, mainly due to its decreased output regarding the approval of new drugs. This can be partially explained by the fact that R&D investments are becoming more focused on areas associated with high risk of failure, where new clinical and therapeutic needs must be met as well as new biological mechanisms must be discovered. This can be characterized as a high risk/high reward situation, coupled with a lot uncertainties and complexities due to the pursuit of innovation in the field of molecular biology. Moreover, three factors must be taken into account when addressing the issues with pharma productivity in R&D, namely development timeframe, number of successful NMEs approved and attrition rate (failure rate in terms of drug development, as compounds do not advance to the next clinical phase). Therefore, it is clear that there are a lot of challenges to overcome in the pharmaceutical industry and the current business format needs to undergo structural reorganization, as it already demonstrates that the R&D model shows signs of limitations. **[4]** The development of new drugs requires a longer period of R&D, because science and technological advancement have progressed to a state where there are no more easy targets to identify and increased competition to exploit new opportunities in the market leads to a decline in pharma productivity. **[4]** This leads to not only higher costs of developing a drug but also increased total R&D expenses, which have experienced a yearly steady rise of 13% since 1970. At the same time, the rate of approval of NMEs has remained unchanged in recent years, resulting in more R&D spend per one NME approved by the FDA. However, this measurement should be taken into account with caution, because it does not necessarily reflect variations in the quality of output. On average, a company produces one NME every 6 years, when two or even three are needed per year for the ROI to make some sense. **[5, 6]** The major cause for the decline of pharma productivity lies in the attrition rate, particularly in Phase II trials, where the survivability rate has shown a substantial decline of 20%. It is poignant to note, that attrition rates can act as indicators of how efficient pharmaceutical companies allocate their R&D resources and constitutes an important parameter for the effectiveness of clinical drug development. There are several reasons that can be attributed to high attrition rates, mainly absence of reliable published data, preclinical models with low predictive accuracy, complexity surrounding clinical trial for treatment of chronic diseases and stringent regulatory guidelines. An extensive review of FDA approvals in 2012 led to the conclusion that the top reasons for failures in phase II as well as phase III are directly associated with lack of efficacy (56%) and varying strategies (7%), while safety issues (28%) are responsible for failures in phase I. In addition, commercial reasons (5%) play also a critical role in decision-making during the clinical phase and often lead to higher type II errors. This means the acceptance of the hypothesis that a new drug will not meet safety and regulatory standards, thus not resulting in a satisfactory ROI when in reality it would have done so if the project was continued further. **[2, 7]**

1.2 Conceptual Framework

The focal point of this research project is the domain of strategic portfolio management (PfM) in pharmaceutical companies. A detailed analysis of internal and external project planning in terms of five parameters (clinical phase, therapeutic area, deal size, number of deals, mechanism of action) of six pharmaceutical companies (AstraZeneca, Boehringer Ingelheim, Merck, Novo Nordisk, Roche, Takeda) will provide a better understanding of the critical process in selecting portfolios that will deliver short and long-term profitability. As discussed in 1.1, it is challenging to choose the correct portfolio due to a variety of reasons, mainly the inability to predict portfolio outcomes. A drug can fail in the preclinical and discovery stages or even in the clinical phases I-III, which is often associated with huge R&D expenses.
The next section, Chapter 2 will present a brief summary of the most important literature findings on PfM and the techniques employed by the management in order to maximize the chances of successful portfolio selection.

Chapter 2 Literature Review

This chapter will explore the methodology of PfM generally within the pharmaceutical industry as well as R&D sector including challenges regarding prioritisation, capital allocation and optimisation. PfM activities are fundamental in improving the operational and capital efficiency of major pharmaceutical companies and overcoming their complexities can lead to not only revenue growth but also higher profitability. Subsection 2.1 will introduce a broad description of what actually portfolio management is and how it directly affects the development of a drug. Furthermore, subsections 2.2 and 2.3 will deal with the concept of portfolio management specifically regarding the R&D department and companies operating in the pharmaceutical sector respectively.

2.1 Portfolio Management

Portfolio management (PfM) can be defined as a dynamic decision process with regular updates and revisions of active new products. While new products are undergoing evaluation and prioritization leading eventually to the selection of the most promising ones, existing projects of a portfolio might be accelerated, deprioritized or even shut down. There is a lot of uncertainty and constant changes in the information flow as well as data analysis during a portfolio decision process in order to achieve strategic objectives. **[8]**
According to the Project Management Institute (PMI), PfM validates that a company can influence its project selection and execution success. Well-structured and effective PfM has the ability to substantially enhance business value by optimizing the arrangement of projects to correspond to the strategic direction of a company, resulting in efficient use of resources (R&D expenses in case of pharmaceutical organizations) and improved synergies among the projects of a portfolio. This is the primary reason that PfM is a critical component and a vital challenge in senior management, which needs multiple decision-making stages to evaluate if a project will showcase commercial success or not, as it is depicted in Figure 2. A general approach towards a singular project within a portfolio would be to divide it into several levels in a decision-tree configuration. Probabilities, outcomes and consequences are illustrated in each stage. **[9]**

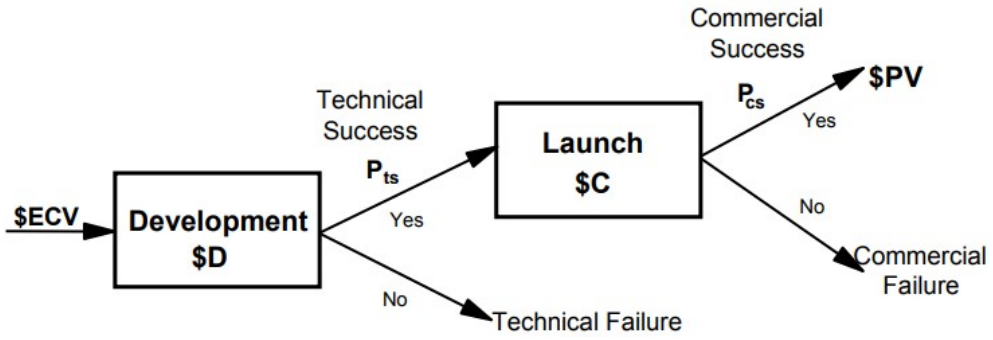

Figure 2: Assessment of anticipated commercial value of a project. [8]

The expected commercial value of a project can be calculated with the formula: ECV = [(PV*P-C)*P-D]

The meaning of the abbreviations in Figure 2 is defined below: **[8]**

$ECV = Expected commercial value of a project
P_{ts} = Probability of technical success
P_{cs} = Probability of commercial success
$D = Project development costs
$C = Commercialization costs
$PV = Present value of project's future earnings

There are four central goals at a macro level that are associated with PfM and will affect the choice of portfolio method. These are:

i) Value Maximization: The maximization of the value of a portfolio can be achieved by appropriate allocation of available resources, which can be accomplished utilizing a variety of financial and scoring models. Most prominent models are listed below. In the end the projects within the portfolio are ranked and prioritized according to the requirements of the desired objectives.

- Net Present Value (NPV): NPV can be characterized as the difference between the present value of cash inflows and outflows over a specific period of time. It is the simplest method, because projects are arranged based on calculated values of their NPVs. Project on the top of the list are considered a Go and the rest are On Hold. However, it is important to elaborate that although a positive NPV is regarded to be a good investment, projects in the preclinical stage are often negative and yet receive funding. In addition, NPV does not take into account risk or probabilities, and assumes that the financial projections are precise. **[8, 10]**
- Expected Commercial Value (ECV): ECV leads to optimization and maximization of the commercial worth of a portfolio by determining the value of each project and taking into account, budget constraints, risks and probabilities.
  ECV has the advantage of identifying the Go or Kill decision process concerning projects as an incremental one and has the ability to penalize projects that require a longer time-period to launch. However, a primary drawback of this technique is the reliance on comprehensive financial and other quantitative data. Moreover, exact estimates for every variable used must be attainable,

which is of course not possible in many cases. A major downside of ECV is its indifference towards the balance of the portfolio and if it has the correct balance of high and low risk projects. **[8,11]**

- Scoring Models (SM): SM are applied when projects need to be prioritized as well as for portfolio management. Projects acquire a score if they fulfil a number of criteria such as: **[8]**

    - Strategic alignment ○ Market attractiveness ○ Technical feasibility ○ Product advantage
    - Reward vs risk

ii) Balance: The goal is to secure the development of a balance portfolio, specifically for projects regarding long-term vs short-term and high risk vs low risk. **[8]**

iii) Strategic Direction: The portfolio must be aligned with the pharmaceutical company's strategy and reflect its targets or objectives as outlined by the top management. **[8]**

iv) Correct Number of Projects: Majority of pharmaceutical companies are undertaking various projects, most of which have limited resources, which leads to pipeline gridlock. This means that projects require longer getting into the market, thus delaying the launch of a potential drug and causing loss in potential profitability. **[8]**

2.2 R&D Portfolio Management

R&D organizations such as pharmaceutical or biotechnology companies can be considered leading users of utilizing PfM, as it is critical in generating productive R&D investments and achieving the desired results. It should be noted that the extension of PfM into the R&D function is complicated and there is a need to select the appropriate models as described above, for an effective and efficient portfolio. **[12,13]**

To increase the overall R&D project value, the management of that project within a R&D portfolio should follow four strategic points: **[14]**

i) Probability-weighted NPV
ii) Long-term vs short-term projects should be balanced in terms of risk, strategic vision and needs of the company
iii) Local versus global business requirement
iv) R&D capabilities, organizational abilities, expertise and resources available

Drug development is a long, costly and burdensome process for the pharmaceutical companies. High R&D expenses, which are primarily ascribed to research costs and low probability of market approval, could be better regulated through a constructive R&D portfolio management. **[15]**

2.3 Pharmaceutical Portfolio Management

Pharmaceutical firms are reputed to be the most mature industries in PfM, as they have plethora of project prospects at each stage of the drug development procedure in order to maintain a

steady pipeline of commercial products. A general overview of the FDA drug development process for reference is shown in Table 1. **[16, 21]** Major pharmaceutical companies like the six that will be analysed in Chapter 3, possess a centralized PfM function with a variety of obligations ranging from strategy development, resource appropriation and decision making. **[17]** The size, culture, structure and corporate governance are all factors that affect to some extent PfM within the pharmaceutical industry, which strives for constant growth rate and sustainability in its R&D operations. **[18]** This is important due to the fact that the degree of variability of productivity levels is correlated to the portfolios and the way they are managed. Therefore, PfM is vital in providing appropriate evaluation of not only the commercial value but also the risk structure of projects that are in development. **[19]** Generally, a standard approach to PfM for pharmaceutical firms would include sizing R&D portfolios as a function of expected revenues and reaching decision on a compound by compound basis. **[20]**

Table 1: Overview of the drug development process.

Preclinical	**Clinical**				**Approval**	**Market**
Toxicology	Investigational new drug application	Phase I	Phase II	Phase III	New drug application	Phase IV/Post market surveillance
		Safety	Safety dosing efficacy	Safety efficacy side effects		
Expenses		$15.2 dollars	$23.4 dollars	$86.5 dollars		
Time		21.6 months	25.7 months	30.5 months		
1 to 6 years	6 to 11 years				0.6 to 2 years	11 to 14 years
Overall probability of success						
		30%	14%	9%	8%	
Conditional probability of success						
	40%	75%	48%	64%	90%	

Project planning and selection can be confirmed at any stage of the drug development process as displayed in Table 1. The goal is of course to decide which project is best fitting to the company's goals and can potentially boost profits. **[21]** There is a certain set of criteria that is taken into consideration when evaluating a project for portfolio selection in the pharmaceutical or biotechnology industries: **[19]**

- Market size, competition, attractiveness ○ Research and development expenses ○ Time of entry into clinical development ○ Therapeutic area strategy
- Clinical feasibility, degree of unmet clinical need

The principal problem with PfM is understanding how to balance increasing expected economic returns with minimizing risk and sustaining heterogeneity in the product mix. This series of trade-offs in overseeing a new product pipeline is given additional complexity with uncertainty in the success of a drug and budget constraints. As previously mentioned in 1.1 the attrition rate increases as a drug candidate is moving along the pipeline. After phase I, about 20% of the

candidates fail and after Phase II, approximately 80% drop out. At the same time there is a surge in financial costs and required resources for testing. **[22]**

2.3.1 Pharmaceutical Portfolio Management Techniques

One of the first PfM methods in the pharmaceutical industry was predicated on economic analysis. Chapman and Ward (1996) suggested that project planning can benefit from initiating a risk management process at the stages in the project life cycle instead towards the end of the final phase. This way a project can be managed effectively and is risk efficient in the corporate sense. **[23]**

The most common used PfM technique is discounted cash flow (DCF), which has the main drawback of not producing enough quantitative details about the risks related to a drug candidate. **[24, 25]** DCF is defined as a valuation method that assesses the value of an investment on account of future cash flows. In case it is above the current cost of investment, then the project could lead to positive results. Pharmaceutical companies usually apply the weighted average cost of capital for the discounted rate, because it considers also the return rate for the shareholders. **[26]**

Moreover, economic analysis methods, although useful, have been criticized for their fixation on single and not multiple criteria decision-making. Thus, Linton, Walsh and Morabito (2002) proposed the Data Envelopment Analysis (DEA) approach, which would be employed to divide a portfolio into three sections: accept, consider further and reject. The 'consider further' group then undergoes greater examination with the help of a subjective method, the Value Creation Model (VCM), which enables the automation of simple decisions, while complicated ones will be given careful consideration. This permits the management of a company to better select/reject a project. **[27]**

Any concerns regarding the economic analysis methods have been addressed by decision theoretic techniques **[28]**, which formalize the main notions of risk and return by interpreting the utility function of the decision-maker. Consequently, the portfolio selection process can be split into two stages: the first stage encompasses observation, experience and the presupposition about the future performance of the projects, while the second stage includes the final choice of the portfolio. **[29]** This formalism allows for compendious PfM methods, such as decision trees, which provide a proper framework for the management to allocate resources pertinent to the possibilities of drug failures. The core methodology behind it is decision analysis, which not only enables the framing of the primary problem, but helps create alternatives. By the representation of various viewpoints and highlighting the value drivers of projects, the efficiency of internal and external project planning is increased. **[30]** A secondary issue with PfM is linked to the number of projects that should be pursued and terminated. Ding and Eliashberg (2002) recommended utilizing the decision tree method structured as a three-stage New Product Development (NPD) pipeline that could resolve the problem. Stage 0, is prior to launching a development project for a new drug. Its market success is reliant on the consumers' needs and the number of other similar available drugs that it will be directly competing with. Stage 1, is the last NPD stage characterized by implementing a binomial distribution of the specific number of successful projects up to this point. Lastly, stage k formulates the expected profit of the concerned projects. **[31]**

However, decision tree techniques can quickly become too complicated and difficult to monitor with an increased size of a portfolio due to substantial number of selection and sequencing decisions. Therefore, Copeland and Antikarov (2001) proposed to present a manageable introduction to option valuation based mostly on variations of the binomial method mentioned in the Stage 1 of the NPD. **[32]**

In fact, Amram and Kulatilaka (1999) have already expressed the idea of substituting the decision tree technique with the real option valuation (ROV), which has received some attention especially in the R&D management and practical investment decisions. In addition, they suggest that ROV can be combined with traditional methods such as DCF or decision analysis in providing real value to corporate growth opportunities **[33]** Pharmaceutical companies already operate in an uncertain business environment, as their growth and profitability are contingent upon the commercial success of its research products. To put this in context, one in 10.000 explored chemicals have the ability to be developed into a prescription drug and even then around 30% of drugs can recover their R&D expenses. Under these circumstances, ROV could enable decision-makers to thoroughly assess the profitability of new projects and construe whether or not to advance to the later phases of a project. **[34]** It should be noted though, that the ROV method is only effective if used on the evaluation of a single project and not an entire pharmaceutical portfolio. **[35]**
Moreover, other PfM techniques such as the stage-gate procedure, is fixated on tactical judgements regarding the regulation of work flow in the drug pipeline rather than decisions of strategic importance associate with project selection. This procedure is a project management tool that splits the time horizon of a project into a few data-collecting sections, which are then divided into gates that serve as information mechanisms to go ahead, hold or terminate a project. **[36]**

Chapter 3 Methodology

3.1 Research Objective

The aim of this research was to explore the way R&D portfolio is managed by biopharmaceutical companies and how project planning is affected. For this purpose, data was provided for six firms: Novo Nordisk, Boehringer Ingelheim, Takeda, AstraZeneca, Roche and Merck. The analysis was undertaken in terms of:

- Therapeutic areas of interest
- Frequency of mechanism of action
- Primary technology
- Stages of transaction occurrence
- Size and number of transaction deals
- Frequency of transaction and asset types

3.2 Novo Nordisk

Novo Nordisk, based in Denmark, is a multinational pharmaceutical company, well-known for being a principal producer of insulin for diabetics and responsible for 40% of the global production. Moreover, it is an R&D concentrated firm, which activities constitute approximately 16.3% of turnover. **[37]** As a successful company, Novo Nordisk recognizes the significance of competent PfM and has emphasized that it attained the world leader status in diabetes care through their “broadest diabetes portfolio in the industry”. **[38]**
Novo Nordisk focuses on transforming unmet clinical needs into innovative cogitations for therapeutic solutions and development of novel biological medicines. From the data provided, it was possible to analyse which therapeutic areas are of particular interest and they are displayed in Figure 3. **[39]**

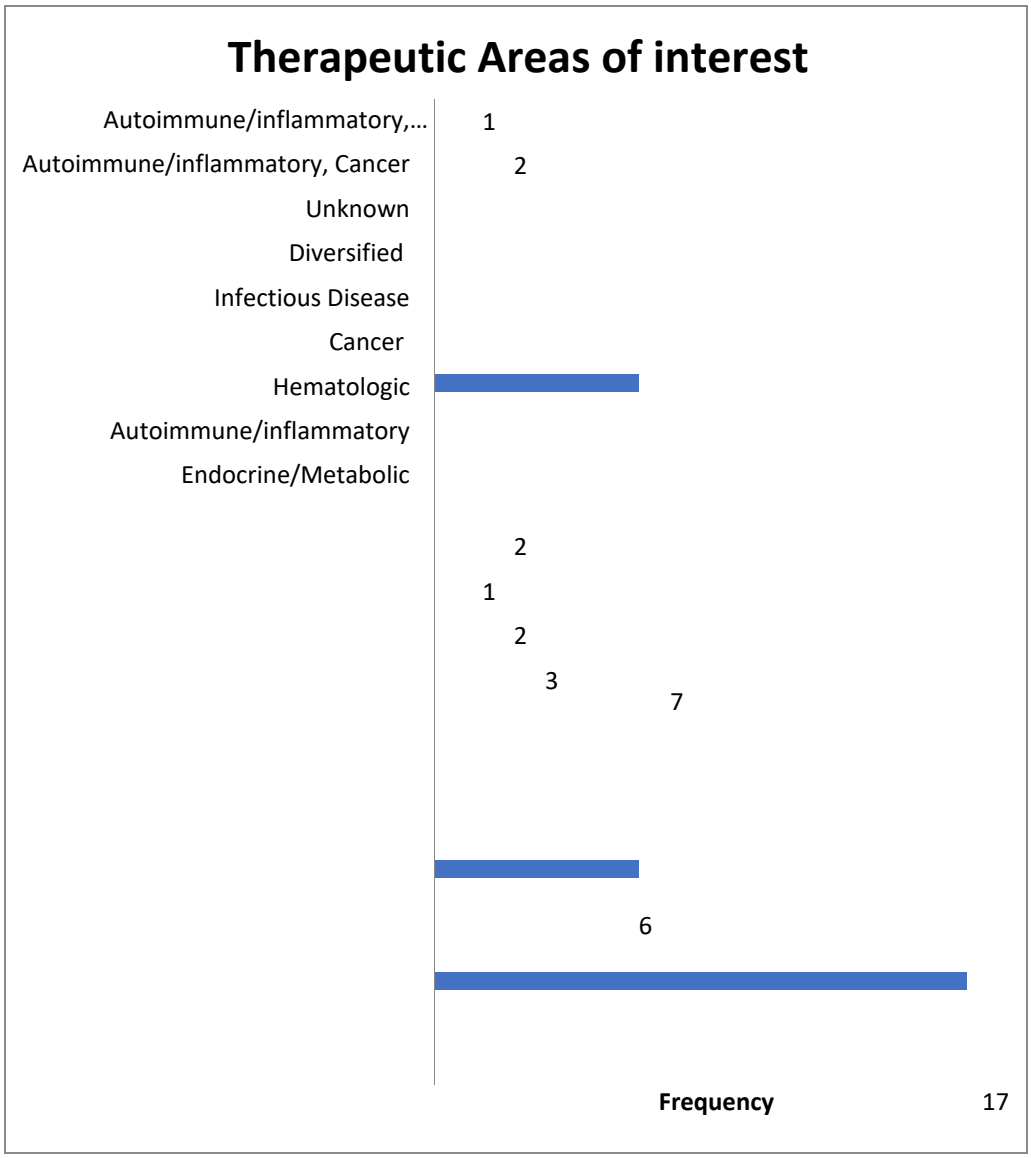

Figure 3: Novo Nordisk's priorities regarding developing new drugs in certain therapeutic domains.

It is evident from Figure 3 that Novo Nordisk invests heavily in combating endocrine/metabolic diseases (frequency = 17) and has a comprehensive portfolio of animal models and compound testing in order to discover new therapeutic methods or drugs. Primary research is specifically undertaken for type 2 diabetes, obesity and non-alcoholic steatohepatitis (NASH), which together affect around 23% of the global population. **[39]** For this reason, early of 2020 Novo Nordisk has additionally allocated $40 million dollars to enhance the groundwork and boost its research capacities in these areas with the hope to introduce more potent drugs in the pipeline. **[40]** The secondary focal point of the R&D is autoimmune/inflammatory disorders (frequency = 6), such as type 1 diabetes that affects 510% of the global population, atherosclerosis that accounts for 85% of all deaths associated with cardiovascular diseases and growth disorders that affect one child in every 3,500-4,000 births. **[39]**

Furthermore, it is logical to deduce that the mechanism of action will be reflected on the therapeutic areas of interest, with activate (agonists) (frequency = 8) and inhibition (antagonists) (frequency = 4) being the most popular, as shown in figure 4.

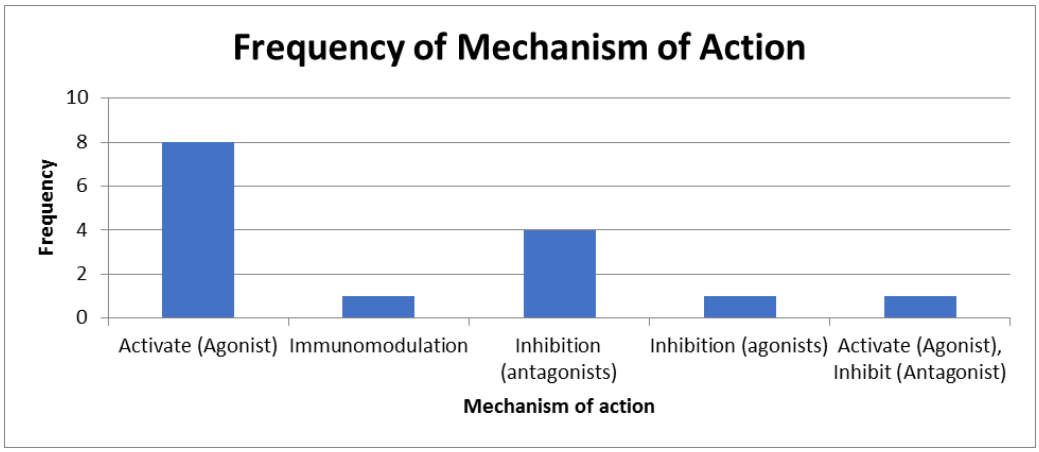

Figure 4: Main mechanisms of action of drugs produced by Novo Nordisk.

Patients with type 2 diabetes as well as people suffering from obesity have witnessed success with glucagon-like peptide-1 agonists (GLP-1), which are considered an alternative to insulin therapy and if combined together can be cost-effective. However, antagonists have also been investigated to be potent as a new therapy for type 2 diabetes. **[41, 42]** On the other hand, inhibition (antagonists) (frequency = 4), such as growth hormone-releasing hormone antagonist (GHRH) are used in type 1 diabetes treatment. **[43]** Both of these mechanisms of action are utilized frequently due to the research concentration of Novo Nordisk in the endocrine and autoimmune therapeutic divisions, which in turn accounts for the majority of its profitability and growth.

There are a variety of primary technologies used by Novo Nordisk in order to discover and develop treatments or products for a range of diseases such as diabetes, autoimmune disorders, and inflammatory conditions. From Figure 5, antibodies monoclonals (frequency = 11), small molecules (frequency = 9) and drug delivery, oral (frequency = 6) are applied the most for drug development and discovery. These technologies are not specifically utilized for a certain clinical phase but generally preferred for the therapy areas of interest of Novo Nordisk.

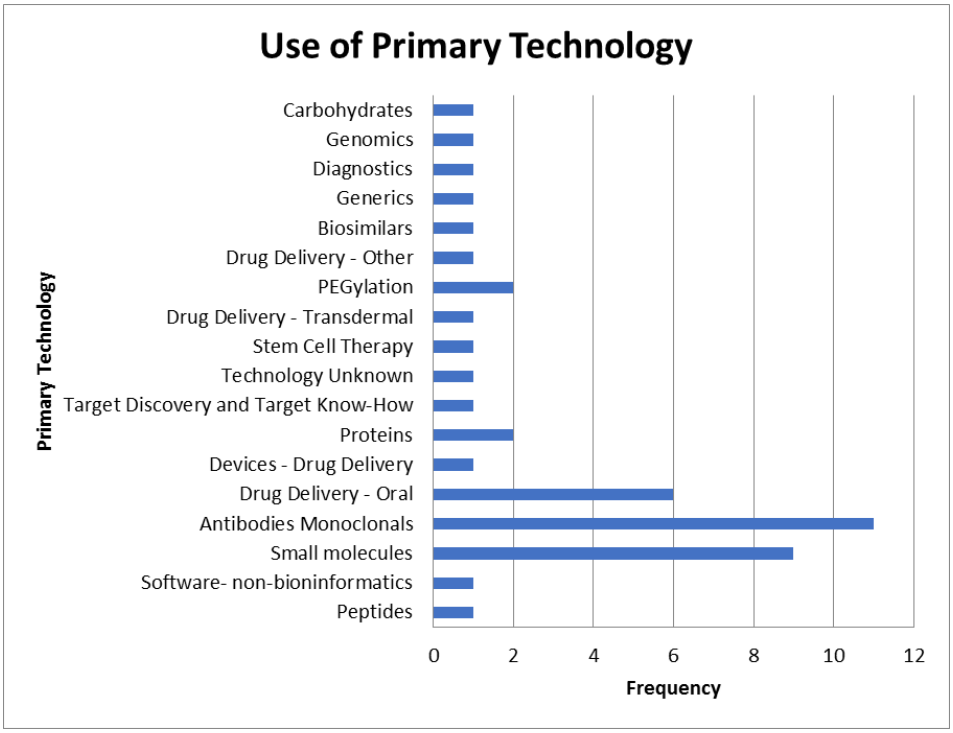

Figure 5: Primary technology used in drug discovery.

Another interesting fact extrapolated from the data analysis was during what clinical phase exactly Novo Nordisk engaged in a transaction. From Figure 6, it is obvious that most

transactions took place during the discovery stage (frequency =16) and preclinical phase (frequency =5), which are associated with high failure rates and R&D expenses. This way the firm can efficiently manage its portfolio by increasing its investments in Phase I and II, which in turn can improve its probability of successfully developing and producing a drug.

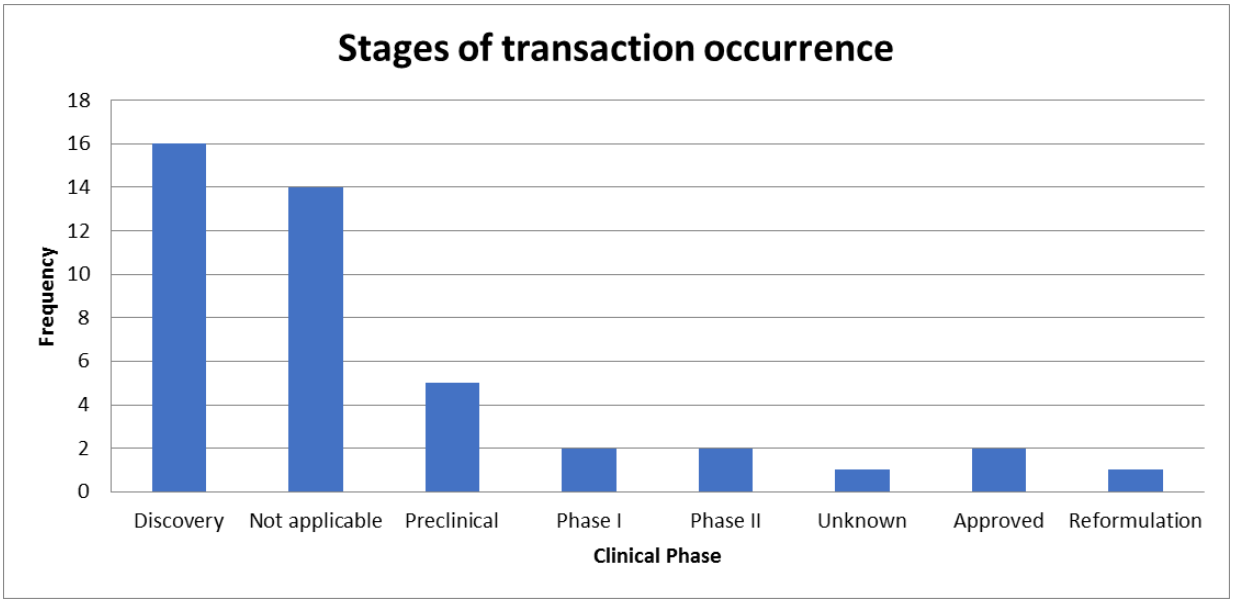

Figure 6: Transaction occasions during different stages of R&D development.

The transaction deals, as displayed in Figure 7, showcase that the majority happened at over $500 million (frequency =4) and under $100 million dollars (frequency = 8). Notable cases include the commercial license agreement between Novo Nordisk and Genmab in 2015 for $502 million dollars for the development and production of bispecific antibody candidates for two medical programs using the DuoBody technology platform created by Genmab. Novo Nordisk presented $2 million dollars upfront payment to Genmab, which also received up to $250 million dollars for achieving regulatory and sales milestones for each exclusive license. **[44]**

Towards the end of 2013, Novo A/S, which is the holding firm of the Novo Group, completed the acquisition of Xellia Pharmaceuticals for $700 million dollars. Xellia's strength lies in the commercialization, development and manufacturing of anti-infective products and therapeutic methods utilizing its fermentation technologies. Moreover, there is considerable interest in its new delivery systems for inhaled or injectable administration through either in house development or partnerships. **[45]**

Novo Nordisk entered into a license agreement with Caisson Biotech in 2012, which gives the firm exclusive rights to utilize Caisson's proprietary technology, which is based on heparosan-based drug delivery system. The aim is to advance its know-how and strengthen its internal research development programs in the area of therapeutic proteins, in an effort to expand its portfolio and clinical pipeline. This will enable Novo Nordisk to not only engineer but also develop drug compounds for undisclosed therapeutic sectors. This deal was valued at around $100 million dollars on the condition that Caisson reaches specific regulatory, clinical and commercial goals as well as sales for products formulated under the agreement with Novo Nordisk. **[46]**

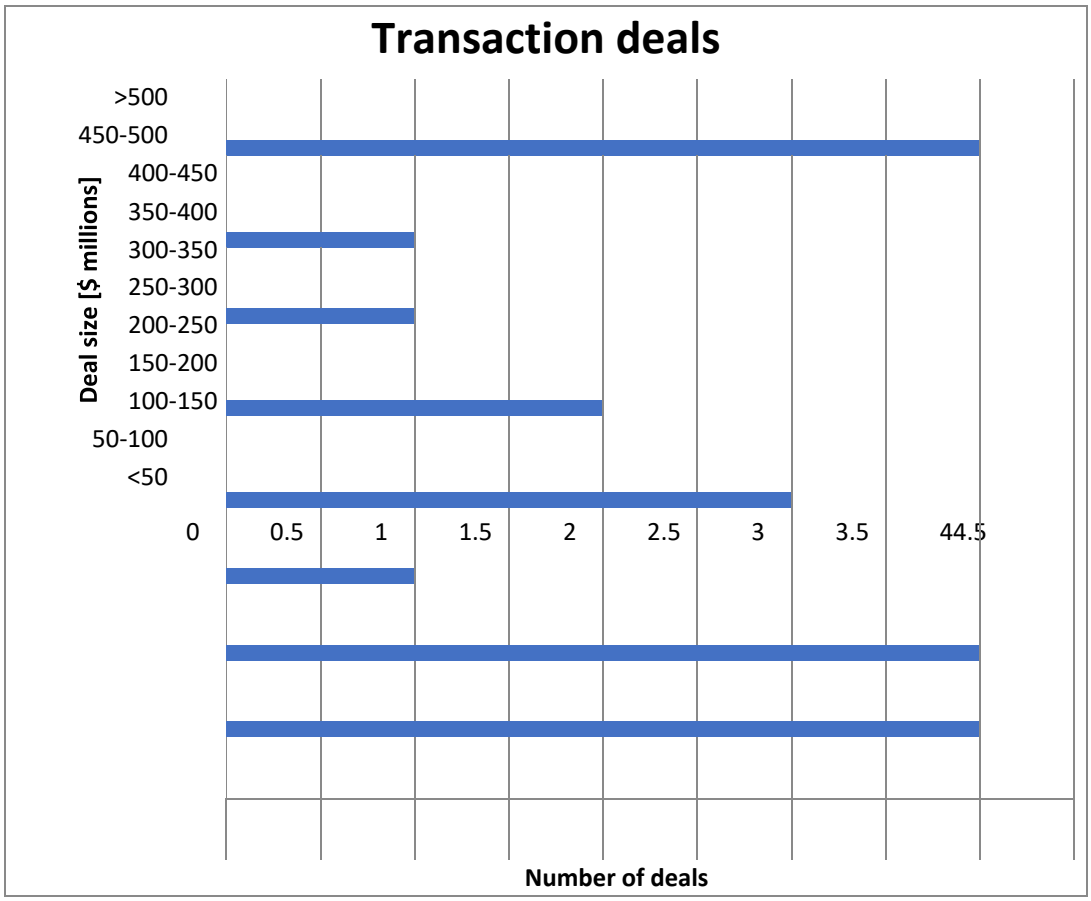

Figure 7: Size and number of transaction deals.

These transactions complement the portfolio of Novo Nordisk, as they have significant investment in major pharmaceutical and biotechnology companies. The strategic acquisitions and deals align with the goal of Novo Nordisk to expand in therapeutic areas where they are the leader in order to further solidify their position and also expand in other business areas by taking advantage of already established management experiences, pipelines and new clinical techniques of developing drugs of other companies.
An interesting observation from the data is the correlation between deals size and clinical phases, which is shown in table 2. It seems that the total amount of transaction deals is greater in the discovery stage with $1,572.12 million dollars and approved stage with $22,300 million dollars than other clinical phases.

Table 2: Size of transaction deals in relation to the stages in drug development.

Clinical Stages	Deal Size [$ million]				
Discovery	175	181.5	295	418.62	502
Preclinical	181.5				
Phase I	57.5	190			
Phase II	32.8	113			
Reformulation	394				
Approved	1300	21000			

A good justification for that is the fact that it is easier to make a deal during the discovery stage for a new novel mechanism or therapeutic method than for a product in the preclinical phase or Phase I, as the commercial success of the potential drug is not guaranteed. To have a better understanding of the main asset types for Novo Nordisk during the clinical stages, Table 3

provides a brief overview. As expected the biggest transactions are undertaken after the development and approval of a drug, where it is possible to sell or acquire an entire business unit or even a company.

Table 3: Primary asset types at each clinical stage.

Clinical Stages	Asset Type
Discovery	Technology
Preclinical	Product
Phase I	Product
Phase II	Product, Company/Business Unit
Reformulation	Company/Business Unit
Approved	Company/Business Unit

The majority of transaction deals involved a licence (frequency = 33), while full acquisitions (frequency = 7) were less desirable, as it is displayed in Figure 8. Looking also into the type of assets involved in those transaction deals, it is shown in Figure 9, that technology (frequency =24) is more preferable than a product (frequency =12) or company/business unit (frequency = 7).

The key driver for those transaction and asset types is the goal of Novo Nordisk to enhance its PfM through balancing therapeutic focus with commercial success. There is a preference for long-term investment in medical therapies, novel treatments and innovative technologies that might prove to be viable solutions for people with chronic diseases. Novo Nordisk still remains the leader in diabetes care with a 29% market share as of 2019 and constantly pursues to acquire exclusive rights and licenses for technologies that might be an alternative treatment for diabetes than insulin. **[47]**

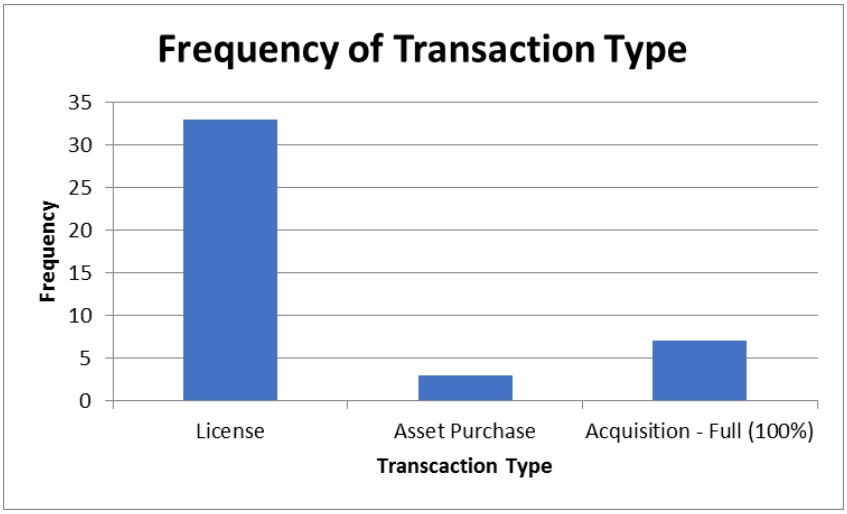

Figure 8: Classification of Novo Nordisk transactions.

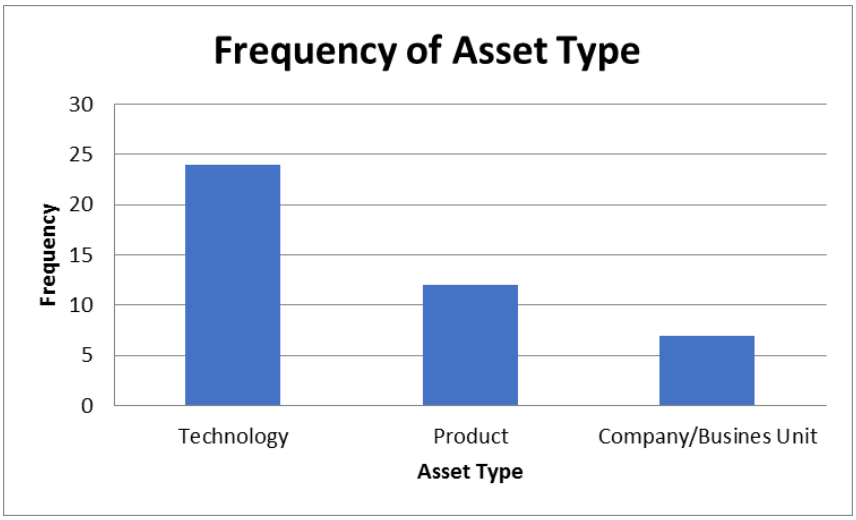

Figure 9: Asset types used in transaction deals.

Furthermore, Novo Nordisk has been constantly exploring to establish its presence in other therapeutic areas such as cardiovascular and kidney diseases through a combination of licensing technologies and acquiring business units. This has proven to be more cost-effective and time-efficient than contributing additional investment into its R&D with an uncertain outcome. Thus, it can enhance and develop a leading portfolio to address medical problems, where it has less expertise and at the same time advance new health initiatives that will lead to commercial success. To have sustainable growth with a strong portfolio, Novo Nordisk capitalizes on innovation development mainly during the discovery stage by partnering with companies and taking advantage of already established clinical methods and original technological techniques for drug discovery. **[47]**

3.3 Boehringer Ingelheim

Boehringer Ingelheim (BI) is a german private research-driven pharmaceutical company with a robust R&D PfM and the goal to provide a better quality of life for humans and animals. The Human Pharma business, which accounts for 74% of total sales, is considered the backbone of BI's overall activities and the Animal Health business positioned BI as the market leader in Germany. BI recognized early on that collaborating with external firms is beneficial in terms of the innovation aspect of its portfolio and leads to more cost-effective methods of identifying new treatments that require high medical urgency. In addition, BI has a broad portfolio in diverse therapeutic areas, as is shown in Figure 10 and aims to further expand it by including approximately 100 preclinical and clinical projects in its pipeline that have the potential to lead to the development of 15 new drugs. **[48]**

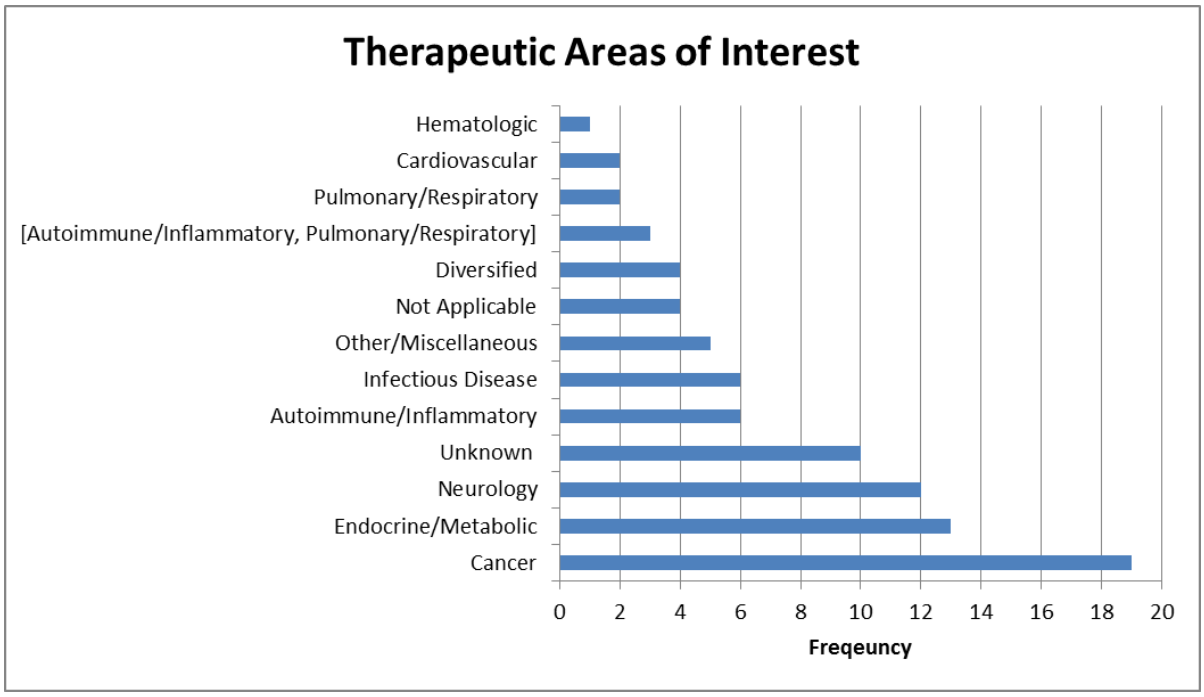

Figure 10: BI's involvement in a range of therapeutic domains.

A major research area of BI, as seen in Figure 10, constitutes oncology, where the R&D is focused on establishing novel cancer cell-directed therapies (frequency = 19) and new therapeutic approaches with the intention to realize cancer breakthroughs. BI is enhancing its research capacity and experience by exploring the most frequent oncogenic drivers, defined as mutations that cause cancer. Although there are no current approved medicines for them, BI believes that successful investigation into these cancer hallmarks can prove beneficial for half of the global patients that suffer from all cancer types. **[49]** The company has already managed to generate two products for the treatment of non-small cell lung cancer and has substantially increased its funding in that area. This is why cancer is one of the cornerstones of its research portfolio and among the most comprehensive at BI. **[50]**

Another important therapeutic area for BI are endocrine/metabolic diseases (frequency = 13) with primary focus on type-2 diabetes, which currently impacts 5.5% of people, but will surge to affect 8.6% by 2040. Therefore, BI is concentrated on the optimization of its clinical PfM in terms of confronting comorbidities associated with diabetes, as they are responsible for the complications of this disease. Even with advanced clinical care, many patients still develop diabetes-related predicaments. **[51]**

The third main therapeutic R&D domain for BI is neurology (frequency = 12) with the research focused on central nervous system (CNS) diseases, such as Alzheimer, Parkinson, Schizophrenia and Depression. There are no modern effective treatments for these neurological and psychiatric conditions, which affect 5.5% of the global population and are the leading cause for the majority of disability-adjusted lives. Hence, BI has expanded its CNS portfolio to include even more projects associated with neurological disorders and is committed through partnerships to address the development of novel medicines. **[52]**

For its considerable research in the area of cancer, which is the dominant sector in the PfM, BI aims to pioneer the development of inhibitors (antagonist) (frequency = 16), displayed in Figure 11, for the discovery of new treatment methods for solid tumors as well as innovative immunotherpaies. **[53]** One of BI's PfM policies is to be transparent regarding its clinical trials, which indicate that majority of its prodrugs in the pipeline, especially in Phase I and Phase II clinical trials, exhibit potent antagonist characteristics and showcase possible successful outcome. **[54]**

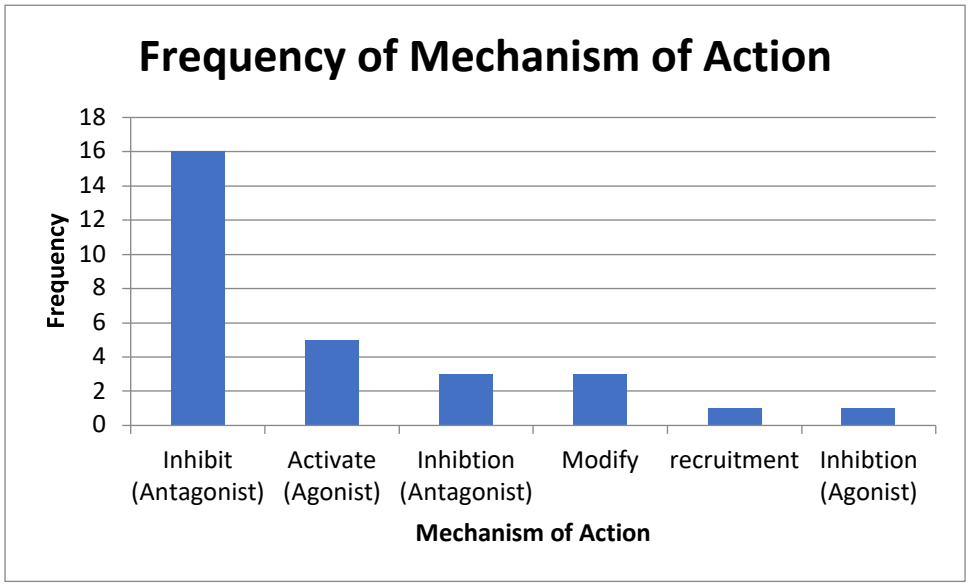

Figure 11: Key mechanisms of action of medicines generated by BI.

BI utilized diverse primary technologies, as illustrated in Figure 12, for the discovery and development of drugs with most prominent ones being small molecules (frequency = 42), antibodies-monoclonals (frequency = 15) and vaccines (frequency =9). Small molecules are often used to identify and characterise drug targets in the expanded neurology portfolio of BI concerning CNS disorders. **[52]** Moreover, small molecules and antibodies-monoclonals (frequency = 15) have exhibited high efficacy in different tumor types by enhancing the immune system response to the presence of tumor-specific mutations. **[55]**

BI has invested heavily in its animal health sector of R&D by constructing a large biotechnology site for veterinary vaccines. The purpose is to further strengthen its strategic portfolio in the area of animal epidemics, which can inadvertently also affect human lives. Therefore, developing and producing antigens as well as vaccines can potentially be lifesaving in the fight against contagious diseases. **[56]**

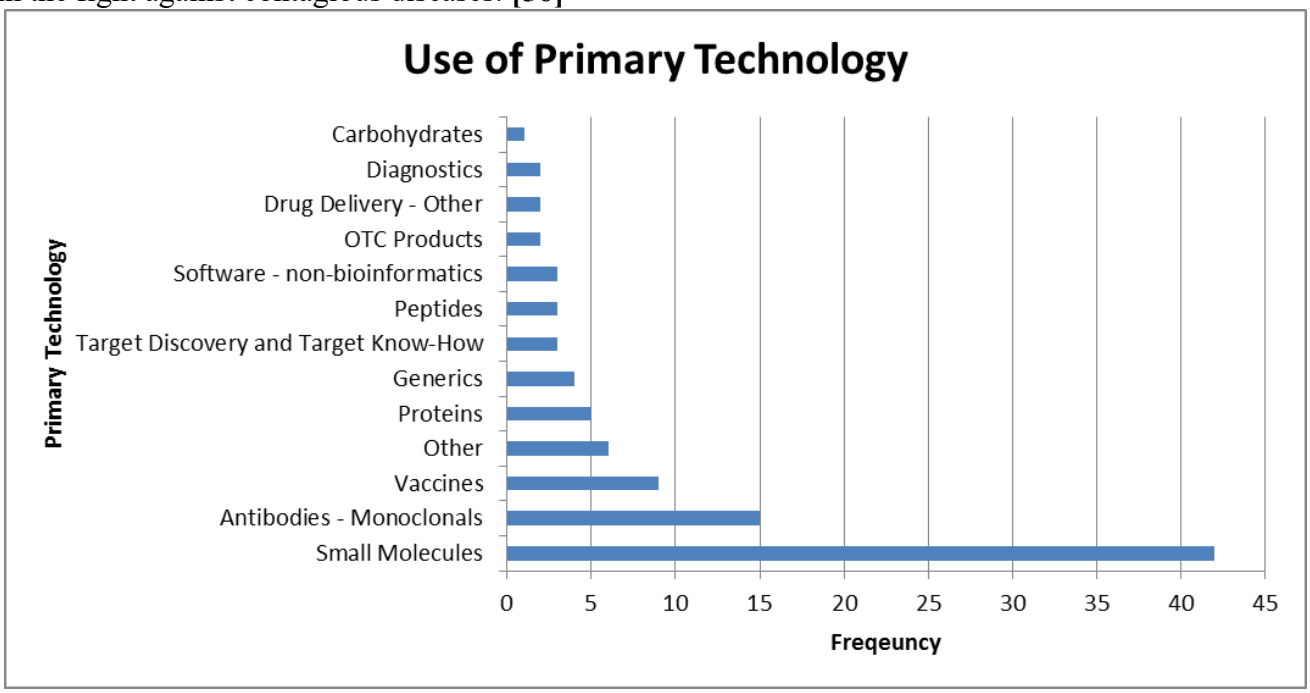

Figure 12: Technology utilized by BI for drug discovery and development.

From Figure 13, it is evident that transaction deals for BI took place mainly during the discovery stage (frequency = 37) and less during the preclinical phase (frequency = 9). BI has shown increased interest in pursuing new therapeutic concepts and treatments for a number of orphan diseases. For this reason it collaborates with other companies in order to use their research and drug discovery competencies as well as already established clinical techniques for drug identification.

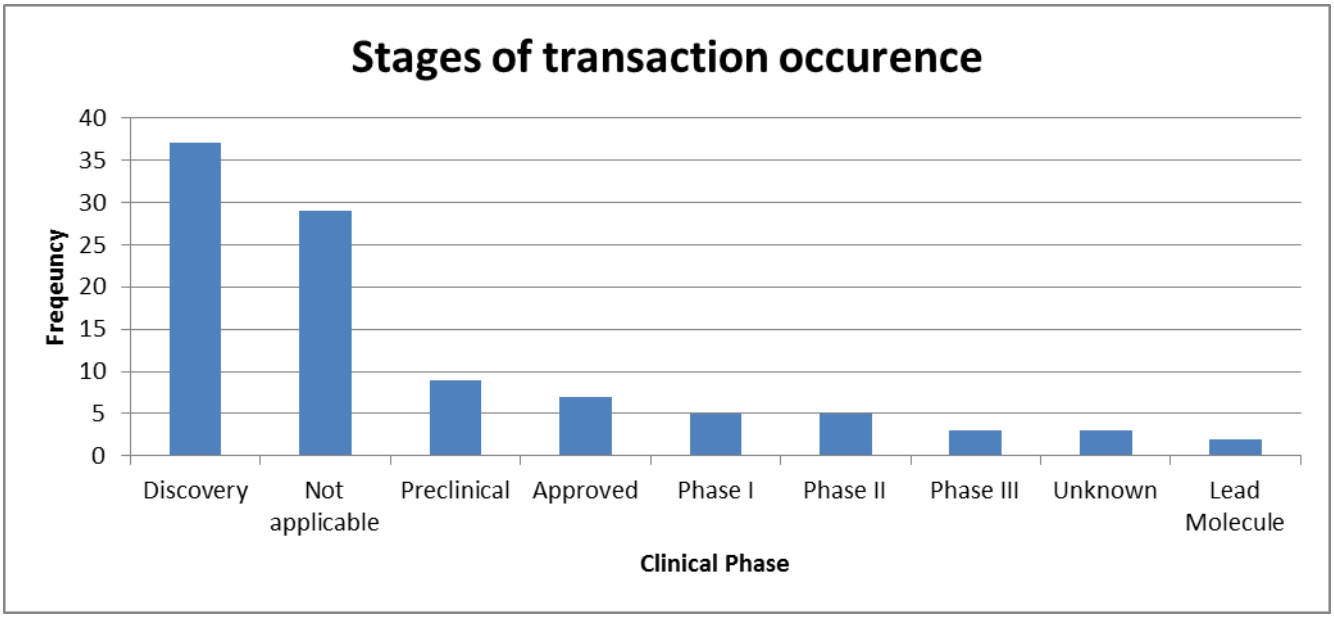

Figure 13: The occurrence of transaction deals during each clinical phase.

The transaction deals, presented in Figure 14, reveal that the majority involved over $500 million dollars (frequency = 15), while the rest was under $450 million dollars (frequency = 16). A major deal valued at approximately $2.65 billion dollars involved the acquisition of Roxane from BI in 2016, which is an American company with a high differentiated portfolio specialised in the development, production and sale of generic pharmaceuticals. This resulted in BI gaining a 16.71% equity stake and acquiring a material position as shareholder in Hikma. Consequently, BI is allowed to invest in Hikma's comprehensive portfolio of 88 diverse products in niche sectors of the pharmaceutical market and also gives it the opportunity to concentrate on its global core businesses in branded medicines and animal health. In addition, the decision was based on the optimization of BI's strategic PfM for generic pharmaceuticals and understanding that it is beneficial in the long-term to enter this agreement with Hikma, as it will provide Roxane with the proper platform to achieve its potential in building a robust pipeline of high-quality medicines. **[57]**

Another important transaction deal valued at around $4.7 billion dollars occurred between Sanofi and BI in 2016, where the companies swapped part of their portfolios in order to enhance their positions in the respective markets. The exchange included the animal health business of Sanofi valued at $13.5 billion dollars and the consumer health business of BI valued at $7.93 billion dollars. This asset swap will enable BI not only to significantly enhance its portfolio of vaccines and anti-parasitics, but also consolidate its position as the second biggest competitor in the global animal healthcare market. It will allow for value creation in the mid- to long-term and facilitate an easier market penetration to major countries. **[58]**

As previously mentioned cancer is the primary research area of interest for BI, thus the partnership with Forma in 2012, which was worth $815 million dollars ($65 million dollars upfront payment and $750 million dollars in pre-commercial milestones), was ideal. Forma has managed to find promising treatment methods against several cancer targets by developing original drug compounds that act against protein-protein interactions, an area that BI has started

to heavily invest in, recognizing its future potential and benefits. Obtaining access to Forma's drug pipeline and more importantly its early clinical development successes, BI has significantly bolstered its cancer portfolio through external project planning. **[59]**

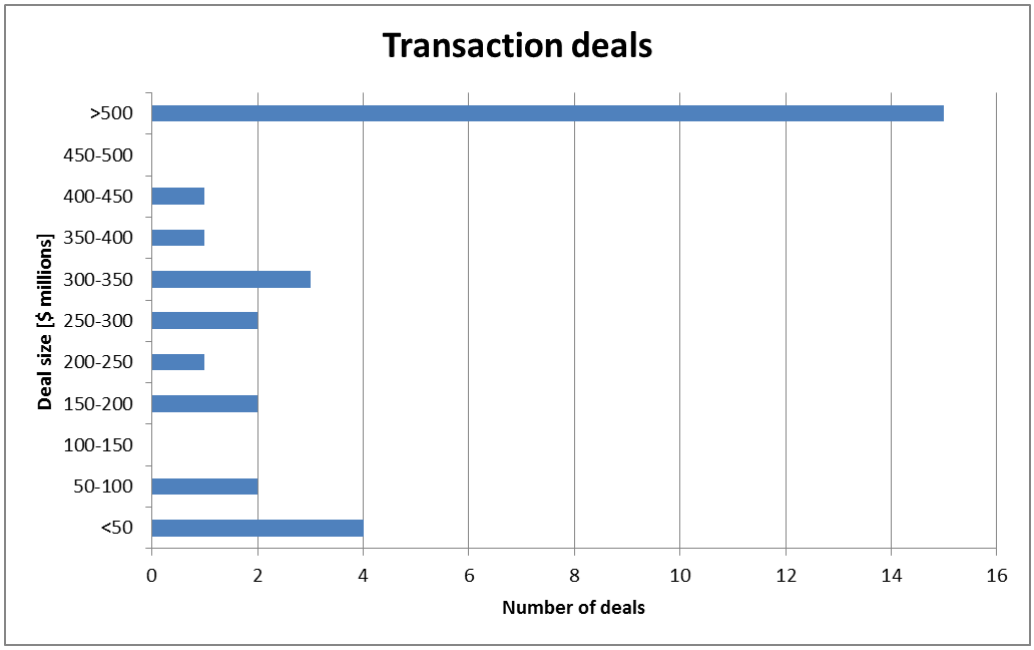

Figure 14: Size and Number of transaction deals.

An intriguing observation point from the data analysis is noticing the preference of clinical stages during which BI tends to conduct a transaction deal. From table 4, the total transaction deal during the discovery phase was $7,815.2 million dollars, while the combined overall deal value of the other clinical stages was $6,335.52 million dollars. BI has recognized that it can strengthen parts of its general portfolio by entering into exclusive licensing agreements at the discovery stage to acquire novel clinical methods of drug discovery or collaborate with research-driven biotechnology companies, which have already found promising drug candidates.

Table 4: Size of transaction deals at each clinical stage.

Clinical Stages	**Deal Size [$ million]**							
Discovery	243	262	354	425	815	1722.7	1823.5	2170
Preclinical	352.7	501.5						
Phase I	30.52	515	601					
Phase II	325	730						
Phase III	33.3							
Registration Stage	2373							
Lead Molecule	336.5	537						

A brief summary of the asset types that BI prefers at each clinical stage is listed in Table 5. BI is mainly focusing on securing access to technology at the discovery phase. An example can be viewed in the collaboration between Exelixis and BI in 2009 in the field of autoimmune diseases, valued at $354 million dollars, for the formulation of S1P1 receptor agonists. The goal was to obtain technological capabilities of Exelixis that enable the identification of compound analogs at an early stage and could lead to the development of therapeutic treatments for people suffering with autoimmune diseases. **[60]**

BI's proclivity for assets in the other clinical stages is product, apart from Phase III, where it also prefers to acquire a company or business unit. A prominent example is BI's purchase in 2012 of the FX125L compound, which has already reached Phase II clinical trials and the somatotaxin programme. This has increased the number of compounds in the drug pipeline of BI that could potentially treat inflammation and lead to the development of products with higher efficacy than any current therapeutic option. Moreover, this could also expand the respiratory portfolio of BI, as the acquired compounds from the somatotaxin programme have the propensity to enhance current therapies against asthma and chronic obstructive pulmonary disease (COPD). **[61]**

Table 5: Preference of asset types during clinical stages.

Clinical Stages	Asset Type
Discovery	Technology
Preclinical	Product
Phase I	Product
Phase II	Product
Phase III	Product, Company/Business Unit
Registration Stage	Product
Lead Molecule	Product

Just as with Novo Nordisk, the predominance of transaction deal types was a license (frequency = 82), as shown in Figure 15, followed by asset purchase (frequency = 15) and acquisition (frequency = 5). BI has always valued cooperation with external partners and companies in the field of early drug discovery and had great interest in receiving access to clinical technology that could identify potential promising compounds. In addition, BI is always searching for prospective in-licensing situations and successful collaborations that would lead in strengthening its cancer and endocrine/metabolic portfolios. **[52]**

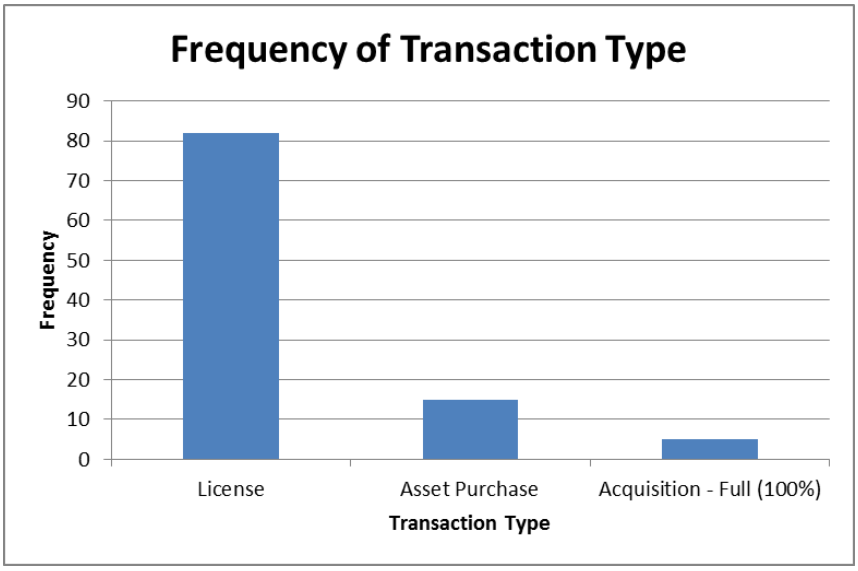

Figure 15: Three main types of transaction undertaken by BI.

BI has approximately 100 clinical as well as pre-clinical pipeline projects, half of which are imbedded in external collaborations. For example the current R&D portfolio contains 13 partnerships out of 28 projects in Phase I and 4 co-operations with biotechnology firms out of 13 programmes in Phase II. The key aim is to accelerate the development of new medicines according to BI's PfM by attaining exclusive rights to innovative technology (frequency = 54)

and even directly acquiring new discovered drug compounds (frequency = 37) that have already undergone Phase I or II clinical trials, as displayed by the frequency of asset type in Figure 16. **[62]**

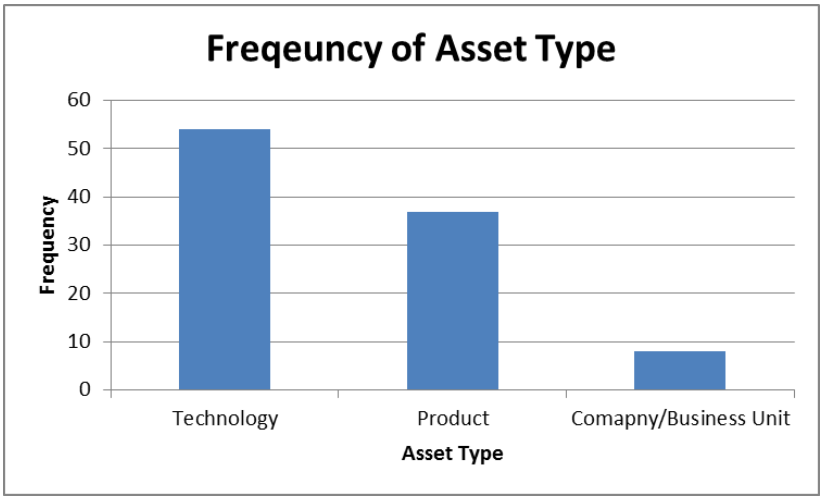

Figure 16: Frequent asset types used in transaction deals.

3.4 Takeda

Takeda is multinational biopharmaceutical company with 48% of the revenue stemming from the US, 20% from Europe and 14% from emerging markets. **[63]** It is a patient-focused and intense R&D-driven organization with core therapeutic domains in cancer (frequency = 22), neurology (frequency = 18), endocrine/metabolic (frequency = 13) and autoimmune/inflammatory (frequency = 11), as displayed in Figure 17. These major business areas lead to a balanced portfolio and are key drivers for the firm's continuous growth, as they constitute around 80% of its total revenue. **[64]**

The primary mission of Takeda's PfM is the maximization of its pharmaceutical portfolio in order to achieve short- and mid-term success by not only fully utilizing its own extensive internal research capabilities, but also actively partnering with biotechnology firms and other academic institutions. Takeda managed to build a robust drug pipeline of novel mechanisms and approximately half of it is earmarked for orphan drugs. **[64]**

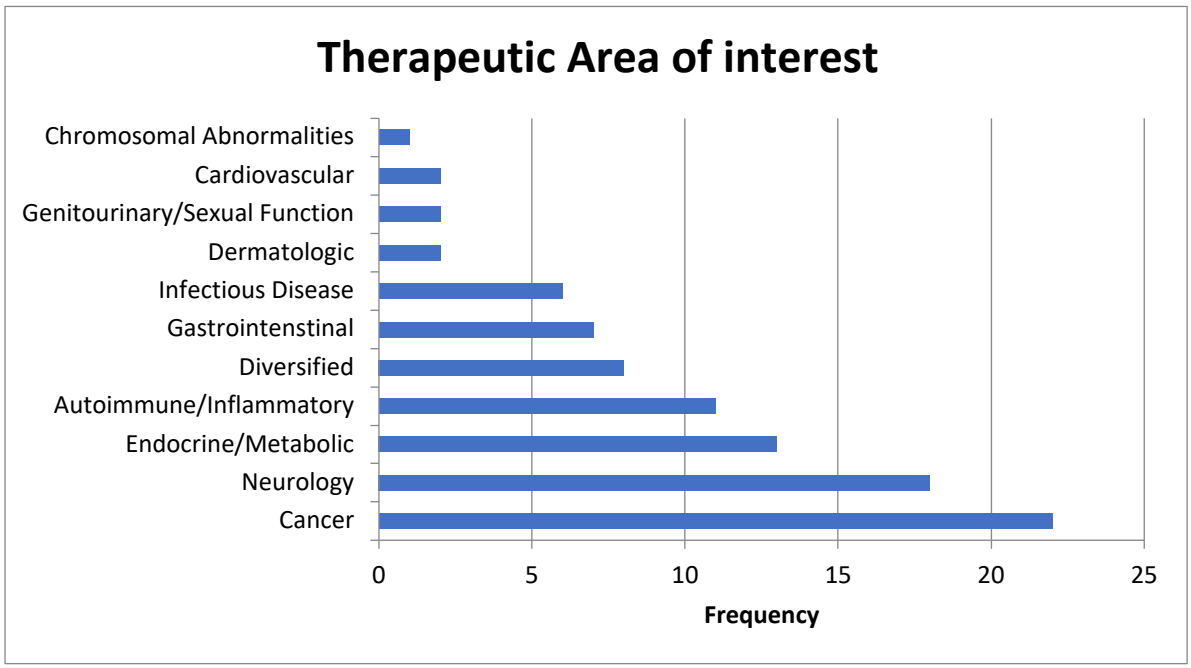

Figure 17: Takeda's main therapeutic areas.

Takeda's existing cancer portfolio expanded significantly after the strategic acquisition of the biotechnology firm Ariad Pharmaceuticals, which specializes in oncology, in 2017 for the value of $5.2 billion dollars. Through this agreement Takeda managed to procure two innovative targeted therapeutic techniques, which enabled it to gain access in the solid tumours medicines market and create a diversified oncology portfolio with global franchise prospects. These early clinical phase assets not only enhanced the scope of Takeda's cancer drug pipeline, but also included new compounds with antitumor activity against non-small cell lung cancer. **[65]**
A further important portfolio of Takeda focuses on CNS treatment, predominantly schizophrenia, depression and specific rare neurological diseases, such as major depressive disorder, binge eating disorder and attention-deficit hyperactivity disorder. This is achieved through innovative digital technologies that can increase trial efficiency by reducing attrition rates during clinical trials and through collaborations with external partner that provide better understanding of the pathophysiology and the underlying biological mechanism that are responsible for these conditions. As a result, Takeda has optimized its neurology portfolio by effective prioritization of promising compounds, thus decreasing the risk of failure at the primal stages of the clinical pipeline. In the short-term the objective is to further broaden its portfolio, while in the long-term the goal is to enjoy innovation-driven growth as a global player in the CNS field. **[66]**
The third dominant portfolio of Takeda concerns endocrine/metabolic diseases with more concentration in immunology, haematology and lysosomal storage disorders, which affect each individual differently and are often misdiagnosed. Takeda has already a well-established portfolio in haematology with an extensive range of high efficacy treatment options across many indications. Moreover, its immunology portfolio comprises of a variety of plasma products, therapies, devices and technological services that can improve the quality of life of patients suffering from rare autoimmune disorders. Finally, its metabolic portfolio has a strong market position due to successful commercial products and promising pipeline compound candidates, some of which were acquired from strategic co-operations with other biotechnology firms. **[67]**

Takeda has directed its research primarily on the studies of Inhibit (Antagonist) (frequency = 29), as displayed in Figure 18. According to the data, this particular mechanism of action occurs mostly during the development of medicines in the cancer and neurology portfolio and less in endocrine and autoimmune project. This is also an indication that Takeda has more commercial success with drugs that exhibit pharmacological effects of an inhibit (antagonist), hence the heavy investments and partnerships with companies that focus on this distinct biochemical reaction.

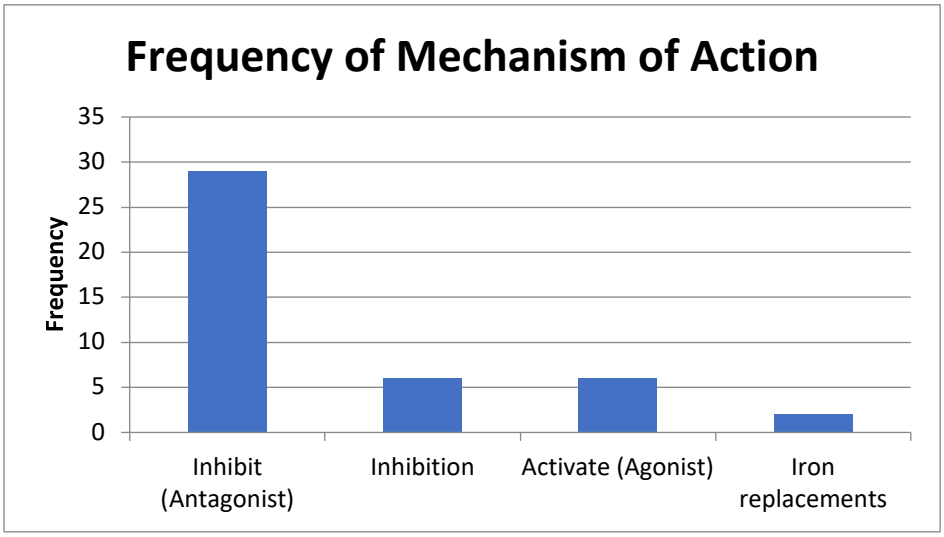

Figure 18: Leading mechanisms of action of medicines generated by Takeda.

The technologies used for the discovery and development platform of new compounds incorporate predominantly small molecules (frequency = 67), followed by antibodiesmonoclonals (frequency = 13) and generics (frequency = 10). Takeda employs chemistrydriven innovative techniques for drug target identification in the field of neurology by adopting a small-molecule based approach. This allows to recognize novel solutions for issues regarding the revelation of promising compounds, improve or at times accelerate the drug discovery process as well as play a pivotal role in the advancement of new delivery clinical tools for the purpose of gene therapy. **[68]**
Furthermore, Takeda has started to utilize more frequently the antibody-monoclonals and antibody-conjugate technologies through exclusive licensing deals in order to develop, manufacture and commercialize anticancer medicines. This is of particular interest for its oncology portfolio and its associated drug pipeline, which has been expanded through the formulation of novel agents. **[69]**

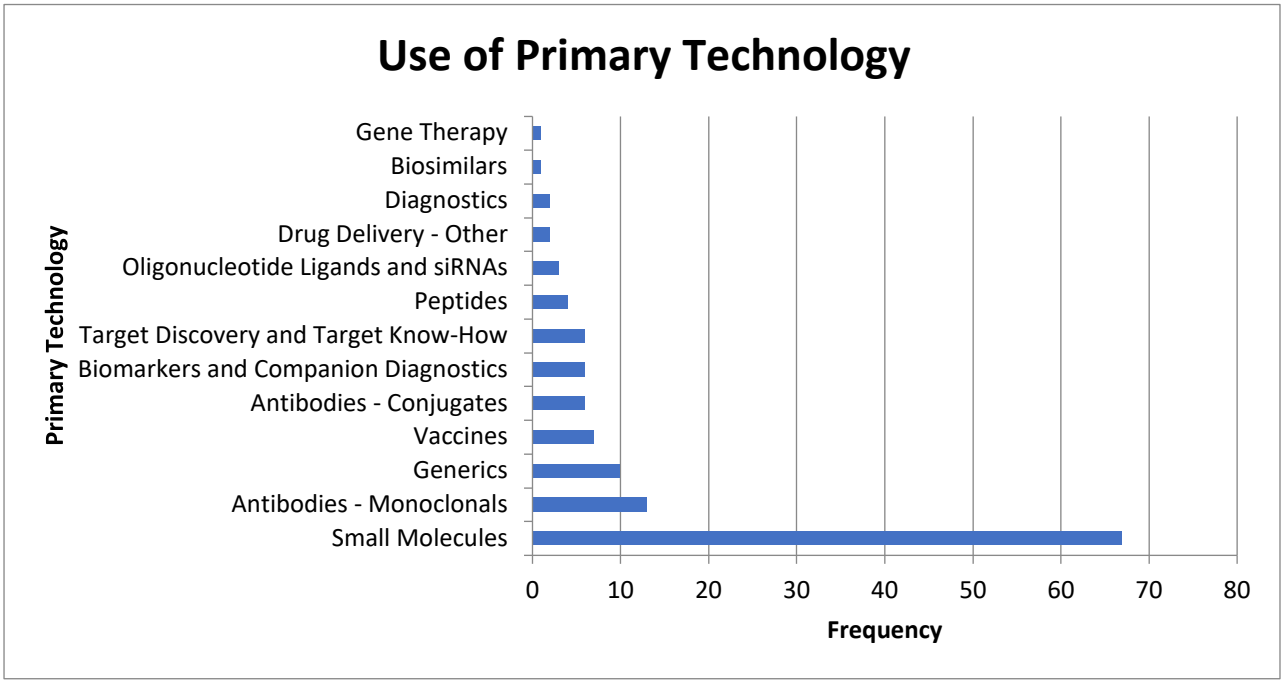

Figure 19: Different types of clinical technology used by Takeda.

The majority of transaction deals for Takeda took place during the discovery stage (frequency = 38) and approved phase (frequency = 25), as it is showcased in Figure 20. Takeda has built a diverse and dynamic drug pipeline by partnering with academic institutions and biotechnology companies in terms of R&D activities ranging from target identification during the discovery stage to drug development and commercialization. In addition, its PfM is supported by an innovative and collaborative ecosystem where pharmaceutical expertise, clinical capabilities and research settings lead to medical breakthroughs, particularly in the progression of formulating effective medicines for anti-cancer and neurological disorders. The R&D of Takeda has already established over 20 partnerships with various healthcare corporations in order to gain access to clinical technologies that can be used for compound screening and identification at the discovery phase of its clinical pipeline. Moreover, Takeda has acquired over 25 companies or business units at the approved phase of a potential successful drug with the intention to either be solely responsible for its manufacturing and commercialisation or to utilize it for further thorough experimental studies for one of its core therapeutic areas. **[70]**

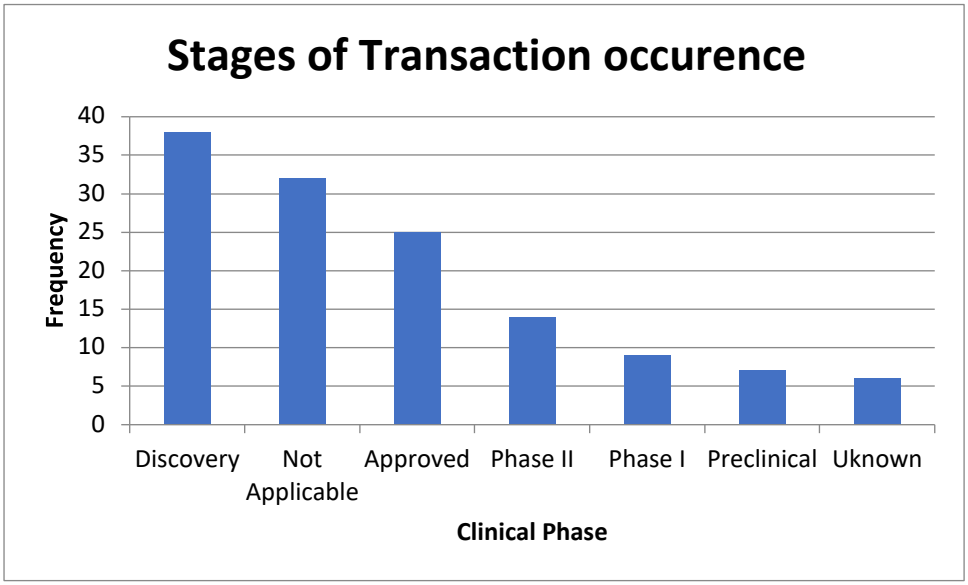

Figure 20: Occurrence of transaction deals during different clinical phases.

The financial analysis of the obtained data, shown in Figure 21, demonstrates that Takeda has engaged mostly with transactions deals worth over $500 million dollars (frequency = 17), followed by arrangements valued between $50-100 million dollars (frequency = 7) and $250300 million dollars (frequency = 6).

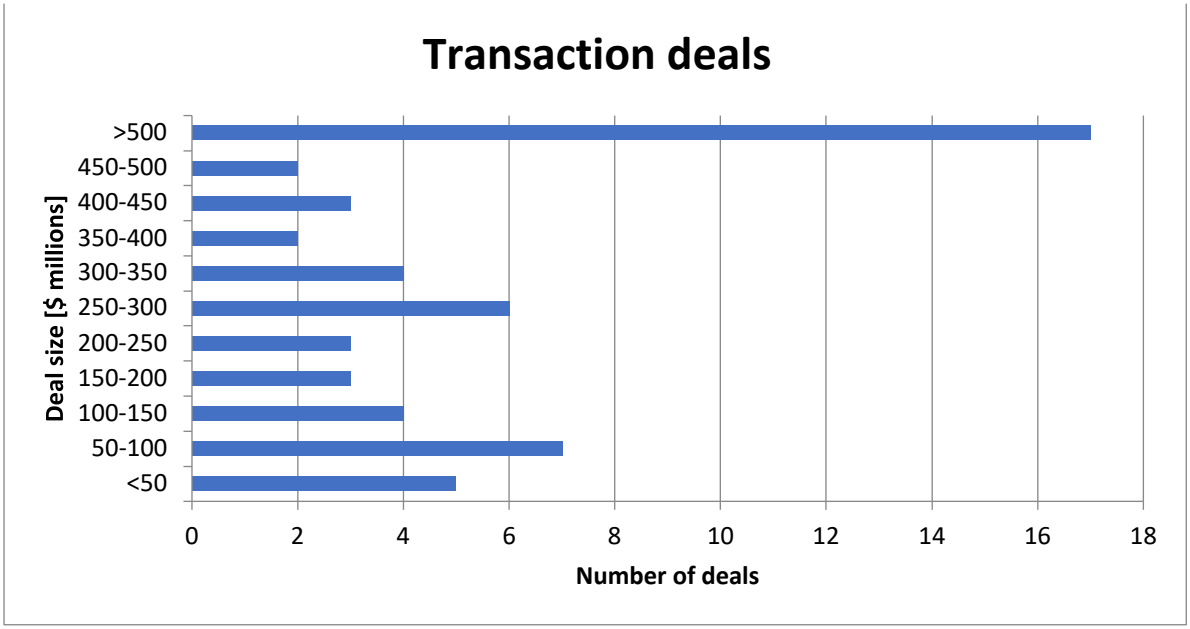

Figure 21: Size and number of transaction deals of Takeda.

One of the biggest deals valued at $13.5 billion dollars and taking place during the approved phase, as shown in Table 6, involved the acquisition of Nycomed in 2011. The agreement gave Takeda access to European and emerging markets with the latter set to become fundamental for the global pharma industry as well as contributed to a steady cash flow at an immaculate time, as it was close to a patent cliff with one of its best-selling diabetes medicine, Actos. Furthermore, Takeda procured the new drug Daxas, used for the treatment of pulmonary disease and obtained a portfolio of over the counter products for metabolic, circulatory and gastric acid disorders. This helped Takeda to expand its drug pipeline with successful leading medicines and further strengthen its overall portfolio with more sales in new markets. **[71]**

The second largest deal on the report of the data, which happened also at the approved stage, was Takeda's acquisition of the biotechnology firm Millenium Pharma in 2008 for approximately $8.8 billion dollars. The contract included the procurement of the entire advanced portfolio of novel product compounds in the field of oncology and inflammation, which bolstered the cancer drug business of Takeda and was responsible for its increased sales growth. Especially drugs like Velcade for the treatment of multiple myeloma (cancer), which is sold in more than 85 countries and encouraging therapeutic methods for inflammatory bowel disease were responsible for the surge in revenue. This move, which significantly enhanced Takeda's global oncology portfolio through attaining differentiated anti-cancer candidates and new research and discovery capabilities, was also aligned with its strategy to be part of the top three oncology pharmaceutical companies by 2020. **[72]** In the discovery phase, the biggest deal was revolved around an option agreement between Takeda and MacroGenics, a clinical-stage biopharmaceutical company, for the exclusive global rights to MGD010, which is based on an innovative dual-affinity re-targeting (DART) technology for the treatment of cancer, autoimmune conditions and infectious diseases. This transaction arrangement valued at $1.6 billion dollars in 2014, was terminated by Takeda due to the reprioritization of its PfM towards strengthening and restructuring its cancer and neurology portfolio. **[73]**

Table 6: Size of transaction deals at each clinical stage.

Clinical Stages	**Deal Size [$ millions]**								
Discovery	100	105.3	200	440	500	790	830	1271	1600
	1600								
Preclinical	64	81	255	488.5	501.5				
Phase I	21.7	310	400						
Phase II	50	125	250	275	294.5	385	620	1265	
Phase III	185	300	320	1177					
Approved	49	66.7	80	167.4	210	266.7	346	400	430
	575	1516.2	1525	8800	13694.4				

The purchase of certain asset types during different stages of the clinical pipeline, as displayed in Table 7, follows Takeda's PfM guidelines in creating a world-class R&D department through a collective approach of internal and external innovation that will lead to the composition of robust portfolios in the domains of cancer, neurology, metabolic and inflammatory diseases. For this purpose, Takeda has acquired a number of clinical technologies from research intensive biotechnology companies in order to accelerate target identification and compound testing during the early stages of its clinical trials. In phase I it usually tends to complete procurement of business units due to a discovery of a promising drug candidate and in the approved stage, the reason is to attain exclusive worldwide rights to a specific compound or clinical technique and thus gain entrance to new markets, as previously discussed. Takeda's central goal is to scale its medicines business in sales and growth, eventually becoming a leading global biopharmaceutical company.

Table 7: Main asset types during individual clinical stages.

Clinical Stages	**Asset Type**
Discovery	Technology
Preclinical	Product
Phase I	Company/Business Unit
Phase II	Product
Phase III	Product

Approved	Company/Business Unit

The preferred transaction type of Takeda, as illustrated in Figure 22, is license agreements (frequency = 106), followed by full acquisition (frequency = 19) and asset purchase (frequency = 11). For the asset type, the data indicated strong inclination towards purchasing a product (frequency = 68), then technology (frequency = 46) and company/business units (frequency = 26), as depicted in Figure 23.
As an R&D-driven firm, Takeda prioritises innovation and novel mechanisms to discover and manufacture commercially successful compounds in its main therapeutic areas. The fastest way to accomplish this objective without needing to bear high expenses is to license either promising drug candidates or clinical technological methods from other pharmaceutical/biotechnology companies. In certain cases, Takeda decided to go through with full acquisition due to the complementary nature of the acquired clinical pipeline for its PfM. **[74]**

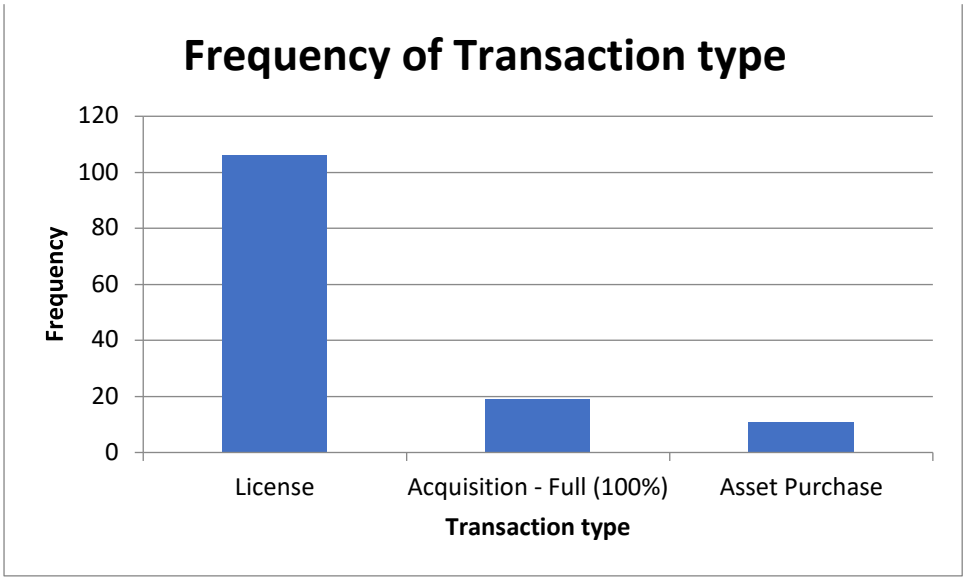

Figure 22: Types of different transactions undertaken by Takeda.

In general, the PfM of Takeda is fixated on developing comprehensive investment strategies that can lead to substantial growth through acquisition or licensing agreements of high quality assets, especially products. Takeda is distinctly focused on long-term profitability with its successful cancer and neurology portfolio, by continuously expanding them through the procurement of technology and sometimes business units. **[65]**

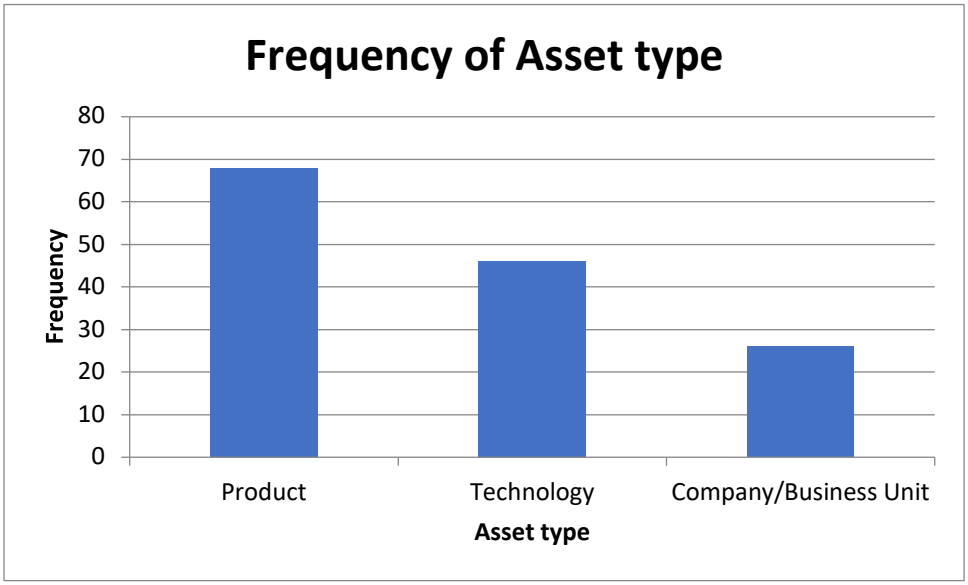

Figure 23: Types of different assets frequently preferred by Takeda.

3.5 AstraZeneca

AstraZeneca (AZ) is a global biopharmaceutical company motivated by innovative science and its entrepreneurial culture to deliver ground-breaking medicines that can provide societal value by improving the quality of life of patients. **[75]** AZ has a large research-intensive R&D department that includes an extensive drug pipeline with a robust and balanced portfolio of approximately 166 projects in different phases of clinical development. **[76]** The three major areas of focus are cancer (frequency = 59), infectious diseases (frequency = 24) and endocrine/metabolic disorders (frequency = 21), as it is illustrated in Figure 24.

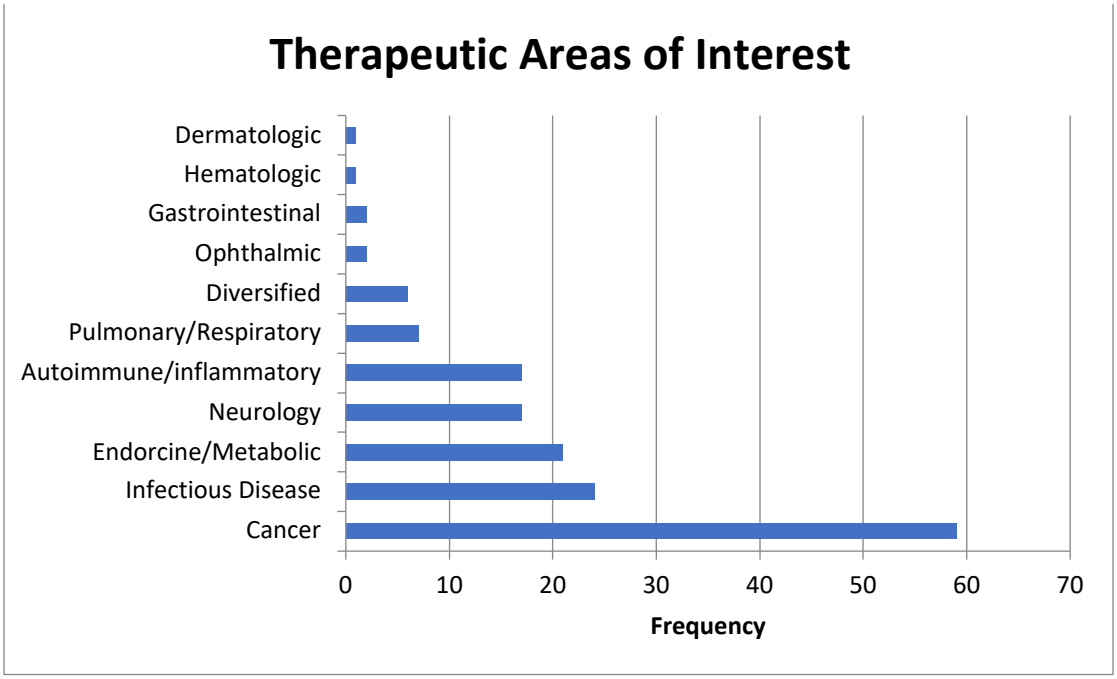

Figure 24: Major therapeutic domains of AZ.

The R&D of AstraZeneca invests a lot of resources in trying to explore new or emerging clinical mechanisms especially for its oncology portfolio, which happens to be its primary focus. Its PfM follows four strategic priorities in order to find appropriate treatments or even manufacture

life-saving anticancer medicines. First, AZ aims to narrow its experimental studies of the biological drivers that cause cancer by redirecting its research concentration on specific scientific platforms, such as cancer drivers, immune-oncology, antibody drug conjugates and damage response. This was intended to optimize its portfolio and improve the successful outcome of the compound development in its drug pipeline. Second, it gives attention to the curative nature of the treatment of patients that are still in the early stages of the disease as well as providing appropriate care to relapsed patients. Third, it uses precision medicine with the aid of biomarkers in order to increase the survival rates in five different tumour types. Fourth, its oncology portfolio is focused to continuously expand the company's presence in other countries so that more patient can gain access to its state-of-the-art therapeutic methods. **[77]**
The infectious disease portfolio is associated with diseases, such as bacterial infections, influenza and respiratory syncytial virus, all for which there are currently no viable antibiotics or treatments. Since infectious diseases are considered to be the second greatest causation of death in the world, there is high demand in addressing these conditions through effective medicines. **[78]** Therefore, AZ has invested considerable funds into R&D of compounds that show inhibit (antagonist) activity (frequency = 66), as they are more prone to recognize specific molecular patterns modulated by the above-mentioned infectious agents. **[79]** Figure 25 also depicts that compounds that exhibit activate (agonist) characteristics (frequency = 15) seem to be also of importance due to their signalling pathway that can lead to activation or suppression of immune responses and thus lead to potentially effective treatments against infectious diseases. **[80]**

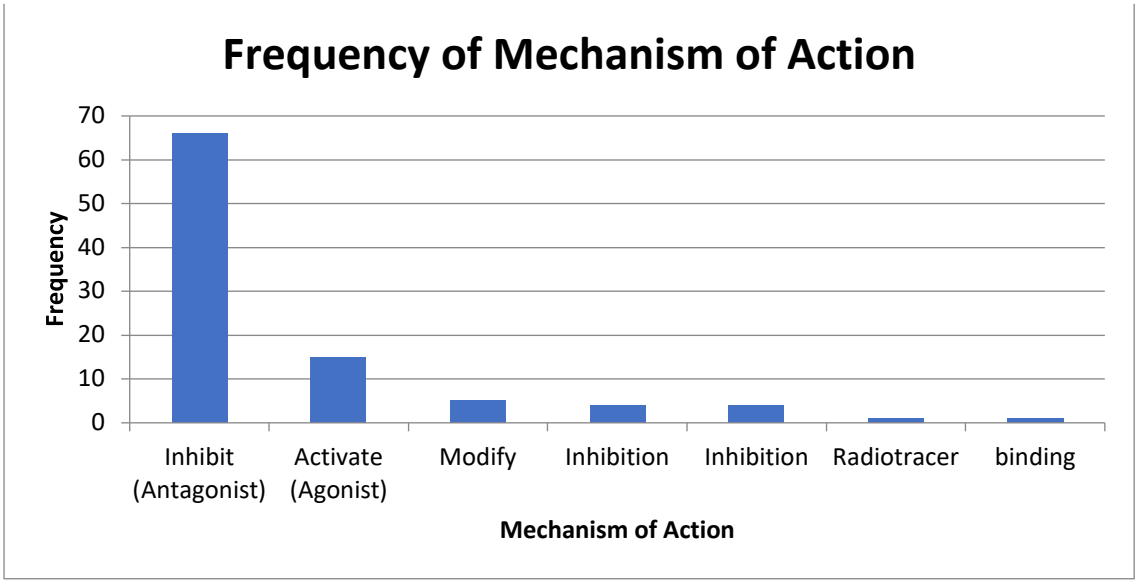

Figure 25: Main mechanism of actions of compounds.

The third major portfolio of AZ has the goal to advance efficient therapeutic solutions for endocrine and metabolic diseases. In particular, clinical projects related to it, utilize extensive mechanistic studies, health economics and enhanced outcomes research in order to identify cutting-edge medical solutions not only for the patients but also for the healthcare system, which is constantly strained due to the surge in affected people. **[81]**
AZ employs a variation of technological capabilities, as shown in Figure 26 in order to discover and develop promising compounds for their portfolios that could be transformed to successfully commercialised medicines. Small molecules (frequency = 93) are predominantly used, followed by antibodies – monoclonals (frequency = 27) and peptides (frequency = 15). Although AZ drug platform is fixated mainly on three technologies, it has embraced a wide range of other novel biological mechanisms, such as proteins, genomics and biomarkers, due to modern progressions in biotechnology. This variety of toolkits of drug modalities enables

the R&D to develop new therapeutic approaches for disorder mechanisms that are regarded as complicated and difficult, like for example infectious diseases. For this reason, the PfM of AZ recognizes the importance of using cutting-edge clinical technology and prioritises small molecules in drug discovery and development. The size of molecules can determine not only the location or the way a compound can act but also the administration route it can take. **[82]**

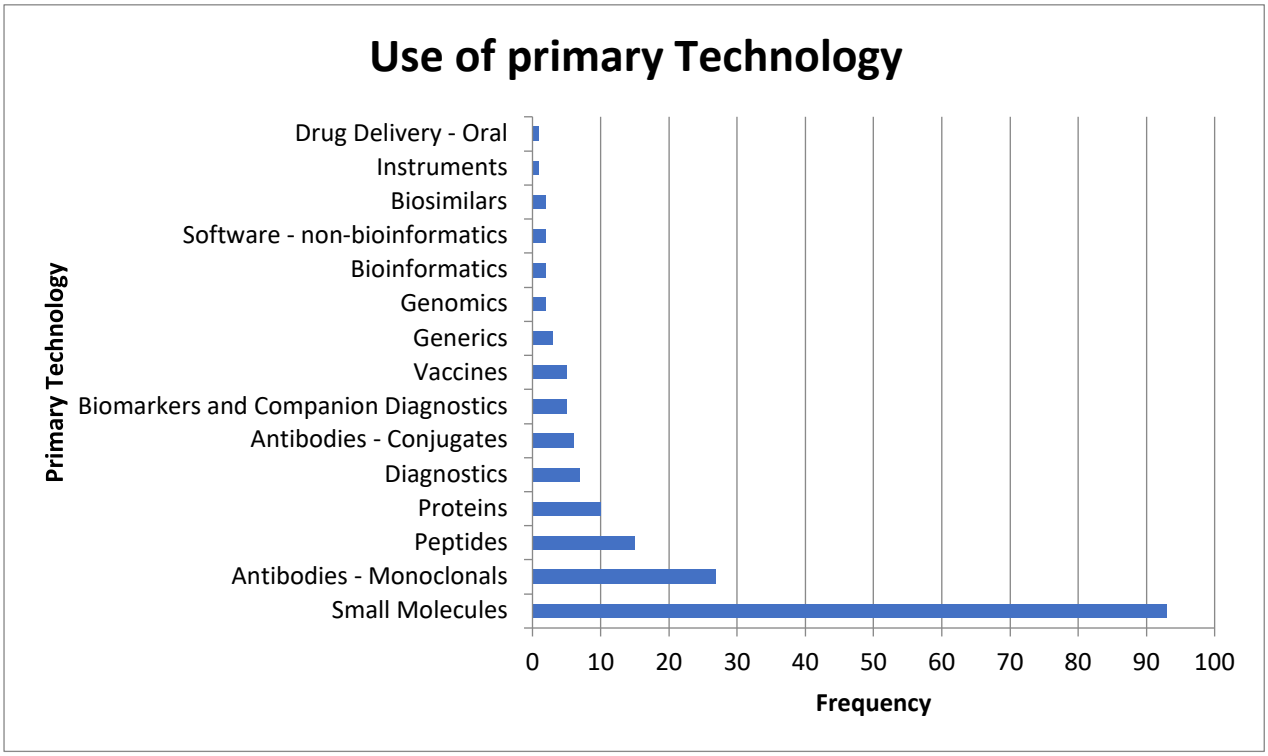

Figure 26: AZ's preference of technology for drug discovery.

Most of the transaction deals occurred during the discovery stage (frequency = 59), followed by the preclinical (frequency = 29) and approved phase (frequency = 26). AZ PfM highlights the need to provide personalised healthcare and medicines so that individual patients can benefit the most. This can be achieved through collaboration with external biotechnology companies in order to incorporate their break-through medical technologies into the development of effective medicines during the preclinical and discovery stage. Generally, AZ has been quite successful between the years 2014-2018 in making successful deals in terms of out-licensing with 66 arrangements in total and in-licensing with 103 agreements. This catapulted the company as the prime dealmaker in the pharmaceutical industry and demonstrated AZ willingness to modify its PfM when necessary through the acquisition of novel drug pipelines as well as promising portfolio assets. AZ out-licensed several assets that were considered not critical for its PfM, but at the same time ensured that patients were able to gain access to them and in-licensed technologies and compounds in order to enhance its major portfolios in the field of cancer, metabolic and infectious diseases. **[83]**

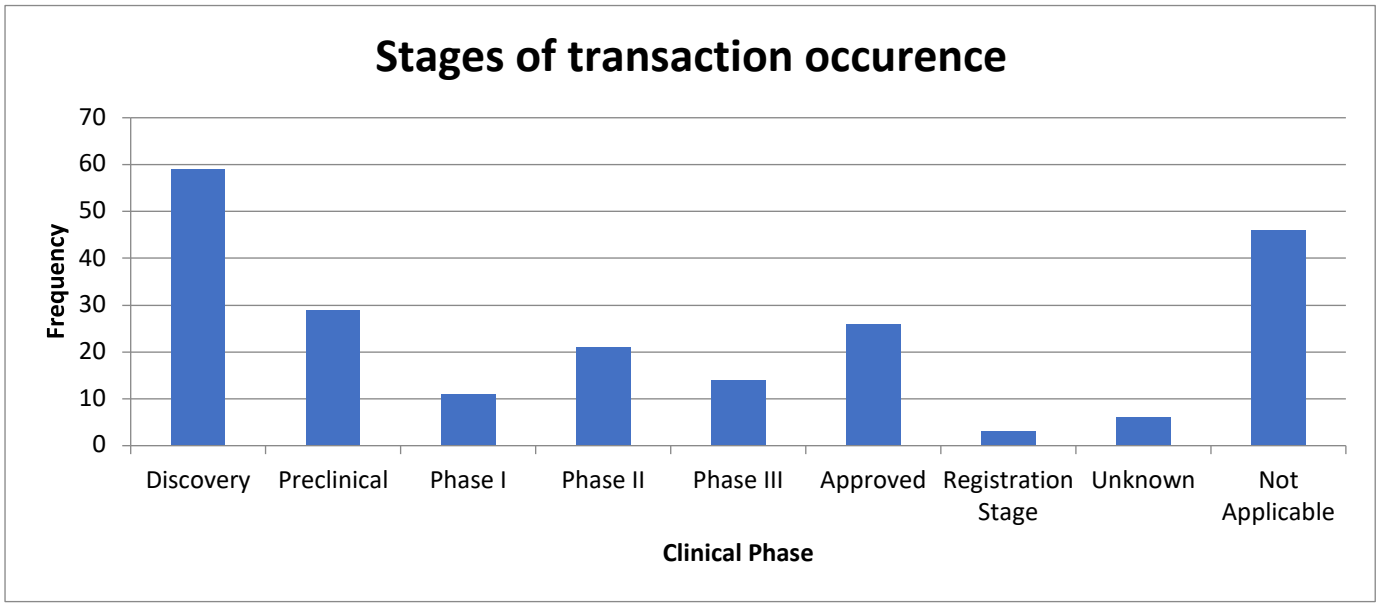

Figure 27: Frequency of transaction deals during each clinical stage.

The financial analysis of data shows in Figure 28 that AZ was mostly part of deals valued over $500 million dollars (frequency = 34). Transaction arrangements in the range of $100150 million dollars (frequency = 10) and $400-450 (frequency = 8) were also important, but did not include core assets that AZ was primarily interested in.

Figure 28: Number and size of transaction deals involving AZ.

AZ biggest strategic deal in the discovery stage was arranged with Isis Pharmaceuticals in 2015 and was value at $4.09 billion dollars, as shown in table 8 due to a mutually agreed milestones and royalties programme. The aim was to develop new therapeutic methods with the aid of antisense technology acquired from Isis Pharmaceuticals for a range of diseases, principally for cardiovascular, renal and metabolic disorders. AZ has realized that treatments based on antisense drugs are clinically effective and therefore they are being developed already in the early phase of the pipeline, in particular in its oncology portfolio. This agreement also makes

AZ responsible for dealing with the regulatory and commercialisation issues of any antisense drug it eventually develops and licenses. **[84]**
In the preclinical phase, AZ entered into an agreement with Regulus Therapeutics, a joint venture company formed from Isis Pharmaceutical and Alnylam, valued at $537 million dollars. The deal concerned the development and commercialisation of microRNA therapeutics, which provide a new pathway of comprehending cellular mechanisms, for a broad scope of disorders, especially focusing on oncology, cardiovascular and metabolic diseases. Regulus would be responsible for the preclinical phase, since it has leading research programmes in those disease areas, while AZ would pursue target compound development as well as commercialise the products on a global scale. **[85]**
One of AZ's biggest deals was the acquisition of MedImmune for $15.6 billion dollars in 2007. From a PfM perspective, this deal was valuable, because AZ was facing certain patent cliffs and suffered several setbacks in its drug pipeline, such as failure of expected blockbusters during clinical trials and missteps at product development of certain licensed medicines. As a counterbalance this procurement allowed AZ to strengthen its product pipeline and expand its existing overall portfolio to include biologic medicine, which are protein-based. This was aligned with its new PfM strategy to promote more biologics and replenish some of its clinical pipelines in order to stay more competitive. In addition, this acquisition bolstered AZ's vaccine portfolio, where prices have experienced a surge, a move that was similar to what Pfizer and Novartis did, both of which entered the vaccine business through acquisitions. **[86]**

Table 8: Size of transaction deals at different clinical stages.

Clinical Stages	**Deal Size [$ millions]**								
Discovery	120	195	310	415	500	1000	4090		
Preclinical	100	145	219.4	267.7	338	414.24	510	537	
Phase I	150	268	400	467	500	874.5			
Phase II	31	50	147	232.25	440	505	727.5	870	1245
	1520								
Phase III	52.1	150	230	443	1115	1260	1350	1645.5	7000
Approved	70	100	223	300	380	618.4	700	886	1575
	2095	3535	4100	7000	15600				
Registration Stage	2700								

An overview of the frequent asset types related to each clinical stage is provided in Table 9, with product being the most prominent one. In discovery phase, AZ tends to license technologies for more efficient target compound identification and in the approved stage it acquires either a product or a business unit/company in order to enhance its portfolio of interest with new promising compounds. For example, when AZ wanted to strengthen its clinical projects associated with respiratory, metabolic and cardiovascular conditions at the discovery phase, it entered into a partnership with a biotechnology company named Bicycle Therapeutics. This deal, valued at $1 billion dollars was arranged in 2016 and would provide AZ with a novel product platform based on bicyclic peptides, which could lead to new potential treatments for the above-mentioned diseases and expand the therapeutic scope of AZ's overall portfolio. **[87]**
An interesting example of AZ procuring a product and a company can be viewed in the acquisition of Acerta Pharma, which specializes in the development of cancer medicines, valued at approximately $7 billion dollars in 2015. AZ wanted to complement its oncology portfolio with a possibly blockbuster drug acalabrutinib, which showed 95% positive response rate in clinical phases I and II conducted by Acerta for the treatment of leukaemia. Thus, AZ hoped it could not only reach its goal of sales revenue of about $45 billion by 2023, but also

compete with the pharmaceutical company Abbvie, which likewise owns a promising drug in its pipeline for the same medical condition. **[88]**

Table 9: Preferred asset types of AZ during the clinical stages.

Clinical Stages	Asset Type
Discovery	Technology
Preclinical	Product
Phase I	Product
Phase II	Product
Phase III	Product
Approved	Product, Company/Business Unit
Registration Stage	Product

As with previous pharmaceutical companies, AZ considers licensing (frequency = 176) as the best transaction method, whereas asset purchase, full acquisition, joint venture and reverse merger are regarded to be less of a priority, which can be seen in Figure 29. AZ utilized licensing mostly with shared responsibilities, where for example it would focus on development and commercialization of a compound and the other company on preclinical identification and discovery. This enables AZ to accelerate the lifecycle of a product and have less R&D expenses.

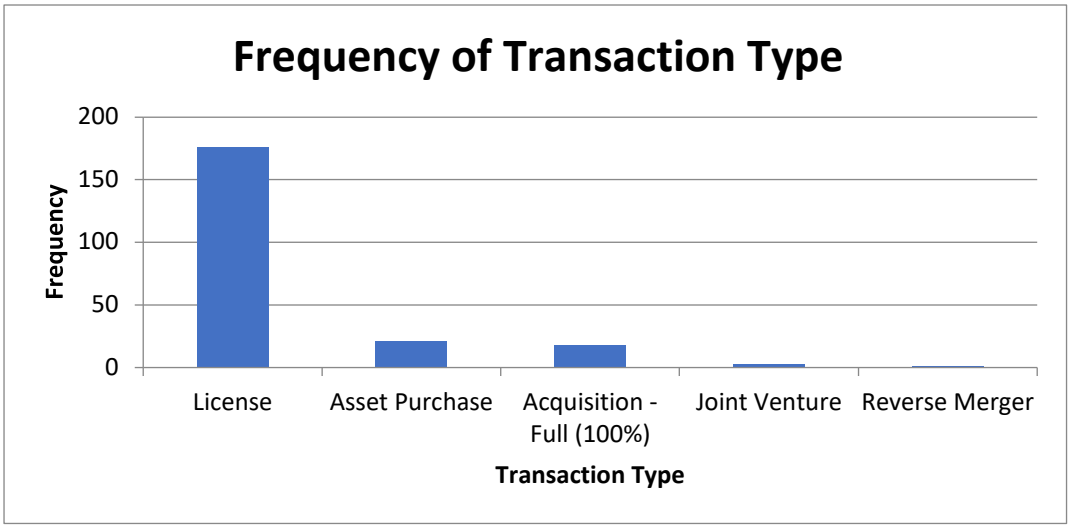

Figure 29: Different types of transaction undertaken by AZ.

Figure 30 depicts that AZ prefers asset types in the form of products (frequency = 111), technology (frequency = 83) and company/business unit (frequency = 22).
AZ intends to be less dependent on its successful oncology, infectious diseases and metabolic portfolios and seeks to continuously expand its overall portfolio with new drugs. Since it has a robust R&D department and extensive technological capabilities for the development of medicines, it is more concentrated on acquiring products that have already showcased promising results from clinical trials, which in turn could transform them to blockbuster drugs and increase AZ's sales revenue by substituting other medicines that are close to a patent cliff. **[89]**

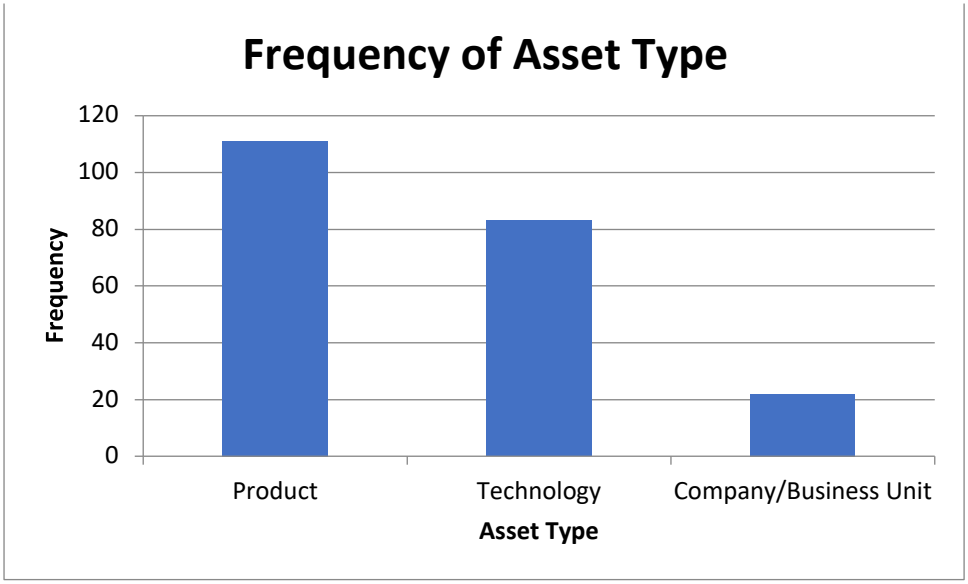

Figure 30: Preferred asset types in transaction deals.

3.6 Roche

Roche is a multinational healthcare company, headquartered in Switzerland with two major divisions, pharmaceutical and diagnostics. The latter is responsible for about two-thirds of the total R&D projects due to the critical data companion diagnostics grants in terms of efficiency and effectiveness of a potential drug leading to the development of targeted personalised treatment for patients. Roche can also be viewed as the leader in the biotechnology sector with approximately half of the compounds in its pipeline being biopharmaceuticals, providing better therapeutic methods and 17 of them are currently available on the market. **[90]**

The most prominent portfolio of Roche is cancer (frequency = 71), followed by neurology (frequency = 28) and infectious disease (frequency = 26), as depicted in Figure 31. The oncology portfolio receives significant R&D investment and is considered to be among the highest in the world with over $9.94 billion dollars, resulting in the development and introduction of nine new anticancer medicines since 2011. Moreover, Roche often collaborates with other biotechnology companies in exchanging scientific knowledge and intellectual property related to cancer research and in some cases tends to procure innovative diagnostic technologies that could aid in improved drug development and treatment monitoring. At the moment the oncology portfolio encompasses over twenty immunotherapy molecules, some of which are promising candidates for drug formulation as well as nine compounds that are already undergoing clinical trials and could potentially address breast, lung and kidney cancer. This shows the breadth and diversity of Roche's oncology pipeline and the company's dedication to find additional efficacious treatment options for the patients. **[91]**

The neurology portfolio is of great importance to Roche, since over 700 million people worldwide are affected to various degrees by neurological conditions from common to the rarest ones such as multiple sclerosis, spinal muscular atrophy and neuromyelitis optica spectrum disorders, which are the three main focus areas. **[92]** Roche has already achieved key milestones with certain neurological medicines that has led to significant improvement in survivability rates after treatment is provided and reduced risk of relapsing. **[93]**

The portfolio concerning infectious diseases is comprehensive and mainly fixated on developing novel therapeutic solutions in three areas: influenza, multi-drug resistant bacteria and chronic hepatitis. For the latter, Roche has entered into a successful partnership with Genentech that enables the licensing and further development of siRNA treatments that seem to be effective. Furthermore, the infectious disease portfolio is continuously expanding through

acquisitions of products and clinical technological capabilities in order to ahead of the evolution of pathogens. **[94]**

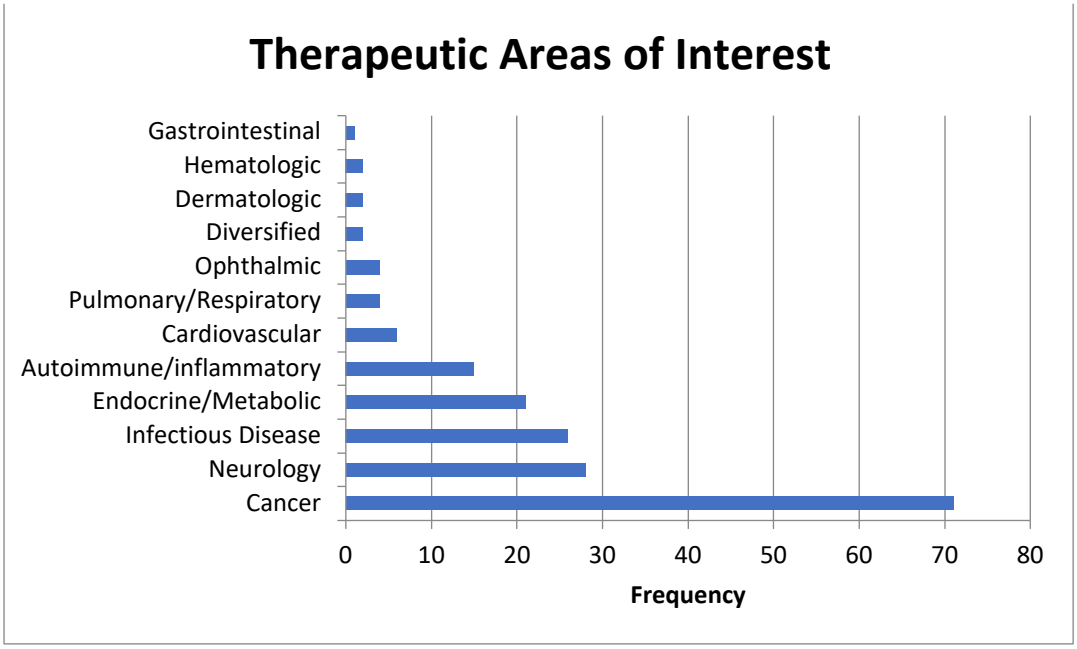

Figure 31: Core therapeutic areas of Roche.

Roche has synthesized a number of compounds that exhibit Inhibit (antagonist) (frequency = 73) behaviour, as illustrated in Figure 32, most of which were designed for the cancer pipeline, since it is contemplated to be its most important portfolio. These compounds have the ability to bind to the targeted domain and after being activated lead to a great decline of cancer cells viability. **[95]**

For its neurology portfolio and in particular for psychiatric conditions, compounds with activate (agonist) (frequency = 7) characteristics have the capacity for efficient reaction with the underlying pathophysiology of CNS diseases. Therefore, Roche has invested in the experimental investigation of these mechanisms in order to better understand their potency and internal pathways, so eventually it can find treatments or medicines that are substantially better than what is currently provided. **[96]**

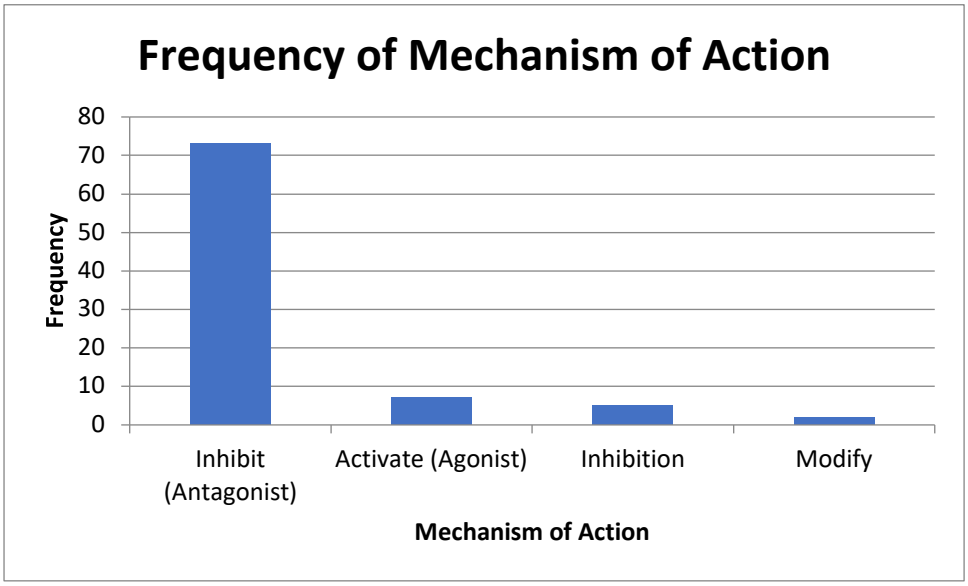

Figure 32: Main mechanisms of action of medicines manufactured by Roche.

Roche prioritized biomarkers and companion diagnostics (frequency = 20) in the process of rapid and accurate identification of which type of cancer a patient has, which is detrimental to the successful outcome of the appropriate treatment. It is also possible with specific biomarkers to be able to detect the appearance of tumour cells before even early symptoms become evident, giving doctors enough time to implement a proper therapeutic approach that will be effective for the patient and cost less for the healthcare system. **[97]**

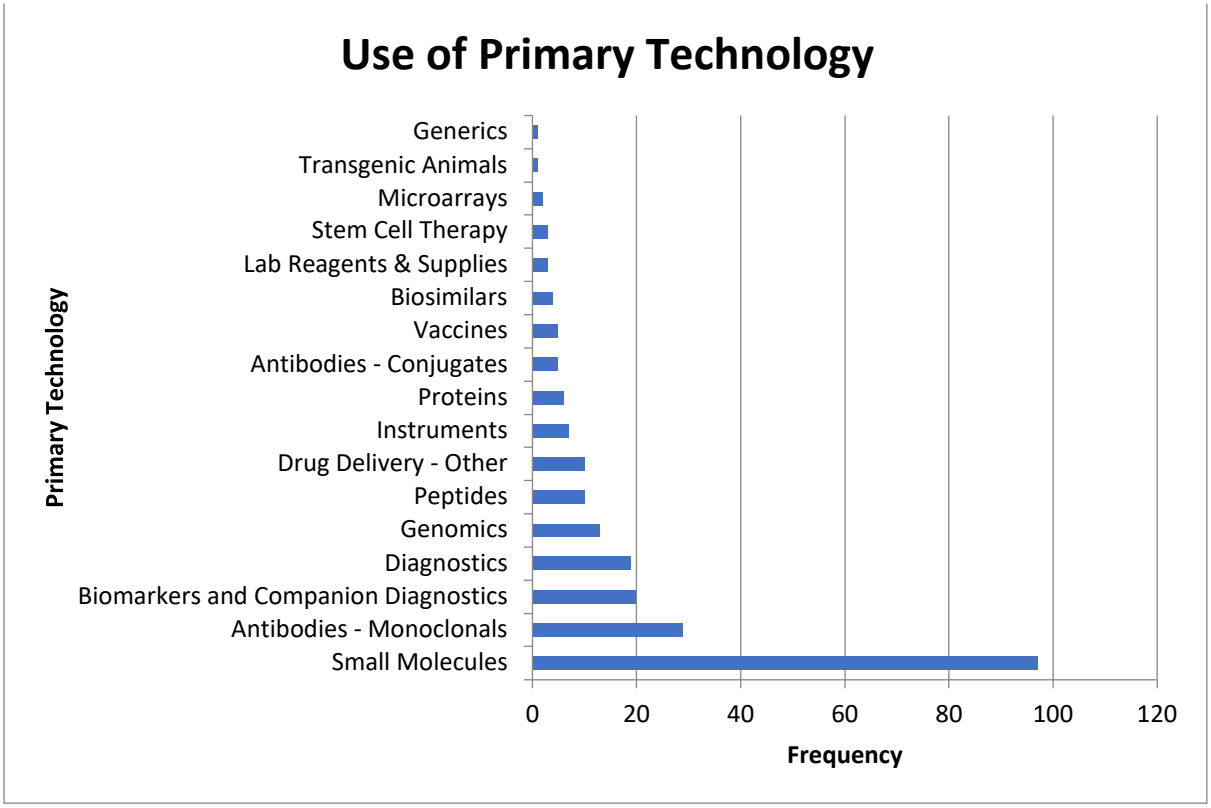

Figure 33: Primary technology used by Roche for drug discovery.

Generally, Roche prefers utilizing small molecules (frequency = 97), as it can be viewed in Figure 33, and has a plan to restructure its manufacturing platform around them by 2021, as it seeks to generate a series of new medicines based on this primary technology. Consequentially, it has initiated a strategy to develop the appropriate launching capabilities for the drugs that will be formulated with small molecules. **[98]** The fundamental reason is to enhance its portfolio of cardiovascular products, as the market is already overwhelmed with generics and the total productivity in this field has steadily declined. **[99]**
Another interesting opportunity that Roche has seized is the technology focused on genomics (frequency = 13), which may pose a certain difficulty in the manufacturing process, but have showcased specificity and high efficacy for cancer, endocrine and neurology diseases. **[99]**

Figure 34 portrays the frequency of transaction deals Roche made at each clinical stage, with the discovery phase (frequency = 60) being the most preferred, followed by the preclinical phase (frequency = 33) and Phase II (frequency = 24). Roche is interested predominantly for licensing clinical technological capabilities at the discovery stage due to its strategic PfM that aims to further develop the early phases of its drug pipeline. For the preclinical and Phase II, Roche leans towards the acquisition of products that show promising potential for it oncology and neurology portfolios. **[100]**

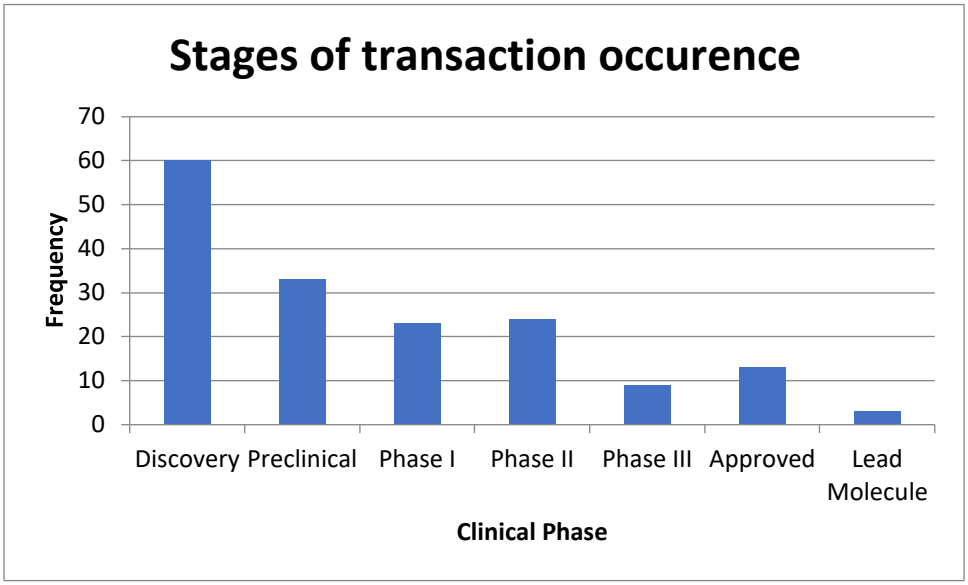

Figure 34: Frequency of transactions during the clinical stages.

The transaction deals, displayed in Figure 35, disclose that Roche was mainly involved in arrangements valued over $500 million dollars (frequency = 37), followed by $150-200 million dollars (frequency = 9) and $350-400 million dollars (frequency = 7).

A crucial deal worth approximately $1.1 billion dollars was composed between Roche and Aileron Therapeutics in 2010 concerning the discovery, development as well as commercialization of peptide therapeutics, which are considered to be an original class of medicines based on stabilization technology. The goal was eventually to find appropriate targets and manufacture medicines in the domains of oncology, inflammation, virology and metabolism, further strengthening Roche's overall portfolio by increasing the number of drugs in its clinical pipeline. **[101]**

Roche also entered into an exclusive agreement, valued at $1,924 billion dollars with PTC Therapeutics in 2009 for the license of its novel and proprietary GEMS technology, primarily in order to treat and effectively manage a number of neurological conditions. The secondary objective was to gain access to PTC's internal pipeline and utilize their expertise in smallmolecule drugs in order to discover novel therapeutic approaches for various oncological, genetic and infectious disorders. **[102]**

The transaction deal with ImmunoCellular Therapeutics in 2009 allowed Roche to license the product ICT-69 antibody that was in the preclinical phase in order to undertake thorough research experiments and determine if it was a suitable compound for the therapy of myeloma and ovarian cancer. This was a move to add a potential promising drug into its cancer pipeline that could lead to increased sales revenue. **[103]**

Roche fulfilled the acquisition of Santaris Pharma for $450 million dollars in 2014 providing them with the locked nucleic acid (LNA) drug platform that enables the discovery and development of new classes of medicines through RNA-based therapeutics. This makes it also easier to find medical solutions for complicated diseases compared to the frequently used primary technologies such as small molecules and antibodies monoclonal. Roche was highly interested in generating highly effective medicines for its oncology and neurology portfolio. **[104]**

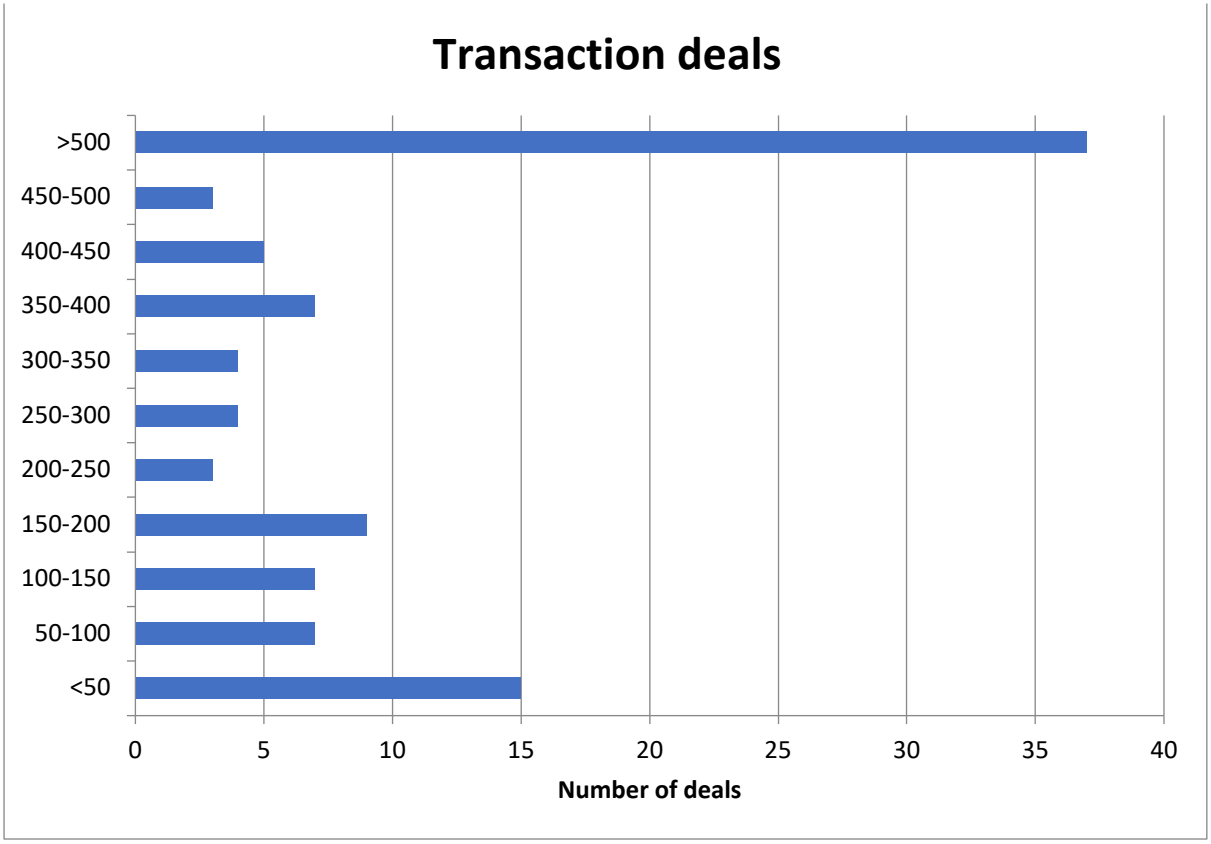

Figure 35: Size and number of transaction deals by Roche.

As previously mentioned, Roche is interested in licensing new technologies at the discovery or preclinical stage, such as antisense or LNA platform for the purpose of discovering novel effective medicines for the treatment of diseases that currently do not have efficient therapies. Thus, the majority of deals are made during earlier stages of the clinical phase, as it is shown in Table 10. At later periods, like in Phase I or Phase II it prefers to own the products manufactured by other biotechnology or biopharmaceutical companies so that it can either further develop them with their R&D department and have exclusive right to commercialise them or combine them with other medicines to create new treatment approaches.

Table 10: Size of transaction deals completed by Roche.

Clinical Stages	**Deal Size [$ millions]**								
Discovery	3.5	83	111	142.5	270	392	400	430.521	588.7
	646	750	1000	1010	1025	1125	1924	2625	
Preclinical	32	182.3	190	363.5	422.5	490	555	600	713
Phase I	31.6	175	310	380.8	535	580	775	830	1150
	1725								
Phase II	41	50	86.2	121.02	175	230	291.6	450	521
	860	960							
Phase III	1.8	135.373	550.6	11200					
Approved	19.56	40.6	176.6	385	607	935	8300	46800	

A brief overview of Roche's inclination towards the type of assets it is looking for at different stages of the clinical phase is provided in Table 11. The majority of them is preferred to be a product, mostly licensed for several years from a biotechnology firm in order to further investigate its potency and determine if the medicine will be commercially successful. In Phase

III and Approved stage, Roche tends to acquire company/business units and thus obtaining direct access to their technological platforms and drug pipelines, enhancing its own portfolio.

Table 11: Preference of asset types at each clinical stage.

Clinical Stages	Asset Type
Discovery	Product, Technology
Preclinical	Product
Phase I	Product
Phase II	Product
Phase III	Product, Company/Business Unit
Approved	Company/Business Unit

Roche is striving to provide a better quality of life for patients suffering from a variety of diseases through personalised healthcare, which can be achieved by researching and developing cost-effective precision medicines. Not only has it developed its own groundbreaking platform of companion diagnostics that is fixated mainly on producing cancer medicines, but it is constantly searching for partnerships and collaborations with other companies, through licensing (frequency = 208) or acquisitions (frequency = 44), as shown in Figure 36, that are specialized in the discovery of novel compounds or possess state-of-theart technologies that aid in the understanding of the underlying mechanism of complicated diseases. As a result, it procures principally products (frequency = 121) and technologies (frequency = 100), displayed in Figure 37, to help improve the quality of drugs in its clinical pipeline and subsequently bolster its sales in case a medicine appears to be efficacious. **[105]**

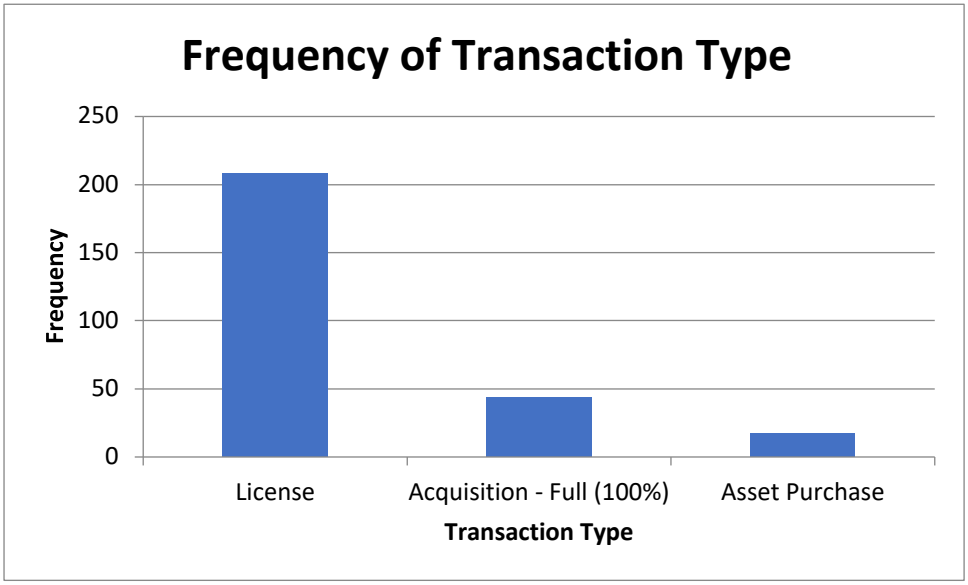

Figure 36: Main types of transaction deals undertaken by Roche.

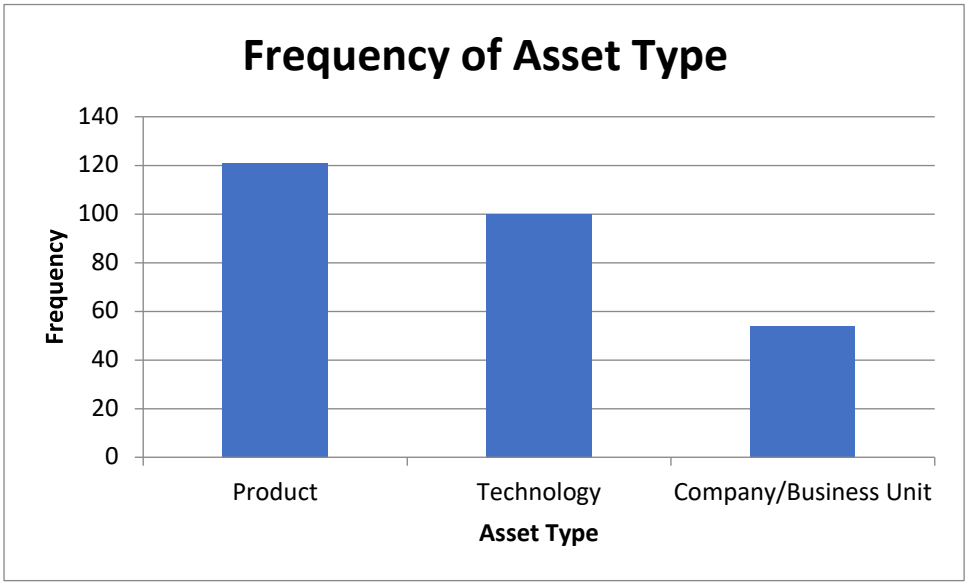

Figure 37: Frequent asset types used in transaction deals by Roche.

3.7 Merck

Merck is a German global multinational biopharmaceutical company that has three core business sectors, namely healthcare, performance materials and life sciences. **[106]** The company has invested more than $9.9 billion dollars in its R&D in 2019, in particular in the field of biotechnology and digital technology that are fundamental parts in advancing the development of precision medicine and discover new way of therapeutic methods for the unmet clinical needs of patients. Merck's PfM revolves around the "Unite for Growth" strategy that will eventually transform it to a leading pharmaceutical company, which will have a robust pipeline with innovative medicine, resulting in $2.38 billion dollars annual sales, and in the medium-term achieve 5-8% growth rate. As a consequence, Merck's overall portfolio is increasingly focusing on the areas of oncology (frequency = 68), infectious diseases (frequency = 43) and immunology (frequency = 28), as is seen in Figure 38, which have become to an attractive market in relation to profitability and prospective growth. In addition, Merck intends to enhance its portfolio by expanding into new geographical locations and strengthening its position in the US and China. **[107]**

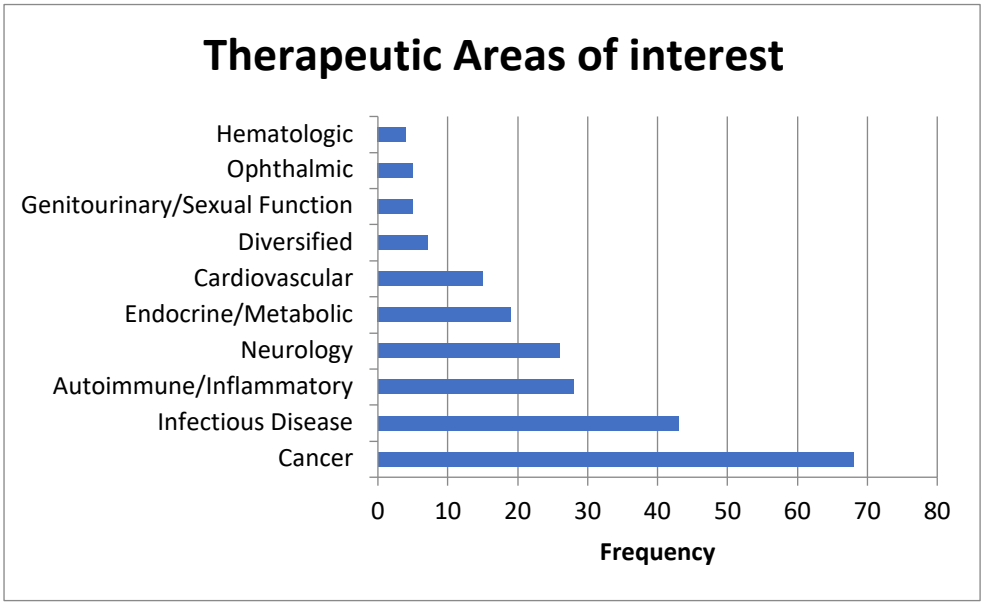

Figure 38: Major therapeutic areas of Merck.

Merck's oncology portfolio is one of its main R&D concentrations, as over 9.5 million people have already died in 2018 and unfortunately the number is continuously rising, despite the treatment progress and numerous medicines being available. It has been predicted that by 2035 approximately 24 million people will be suffering by a certain type of cancer, thus the aim of Merck to find effective cancer treatments through a combination of heavily investing into its R&D and partnering with leading biotechnology firms in the field of cancer research. The present treatment approaches towards cancer projects involving head/neck, colorectal and lung are based on compounds with inhibit antagonist (frequency = 70) characteristics, followed by activate agonist (frequency = 15) behaviour, which are also successfully utilized in immunological projects. **[108]**

The infectious disease portfolio is the second largest at Merck, which was one of the first pharmaceutical companies to contribute in the development of antibiotics and has also undertaken pioneering studies into HIV and its underlying mechanism. In addition, Merck has been able to create robust R&D programmes that are dedicated to find solution for a variety of infectious diseases and are constantly monitoring global tendencies regarding antibacterial resistance by developing novel vaccines and medicines. **[109]** There are currently nine compounds at late stages of its drug pipeline with promising potential that are based on inhibit antagonist mechanism of action, sixteen compounds at Phase II and Phase III of clinical trials, some of which are prone to activate agonist and inhibition behaviour and three products that have already received approval. **[110]**

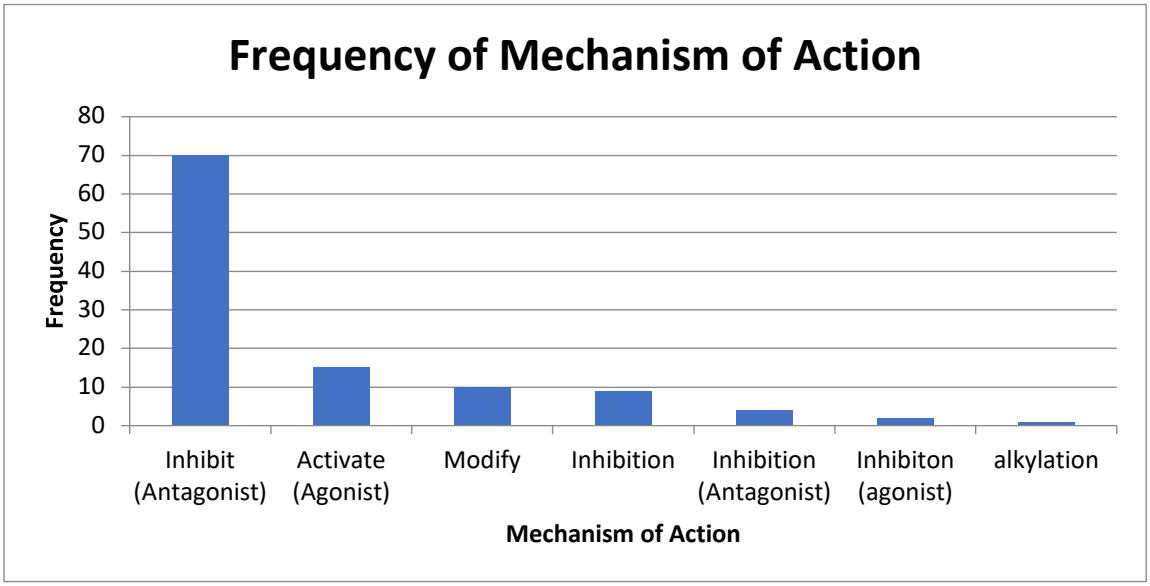

Figure 39: Mechanism of action of medicines manufactured by Merck.

Merck utilizes a number of advanced technological platforms for drug discovery and development, primarily small molecules (frequency = 125) and antibodies-monoclonal (frequency = 32), as shown in Figure 40. There has been a trend the last years on directing R&D departments across many pharmaceutical companies to focus on the advancement of small molecules and significant investments have been made to further amplify their advantage. Merck uses small molecules to identify new targets, find new pathways for drug interactions and compound profiling for all of its portfolios. For this reason, in 2019, Merck acquired Arqule, an oncology company specialised in small molecules approaches for around $2.7 billion dollars. Compounds developed via small molecules processes are cost less compared to using generics or biosimilars, which results in higher profitability. This move has the same reasoning behind the acquisition of Loxo by Lilly and Array BioPharma by Pfizer. All these big pharmaceutical companies envisaged to enhance their cancer portfolio with a series of clinical-stage compounds that would contribute positively to their respective sales revenue. **[111]**

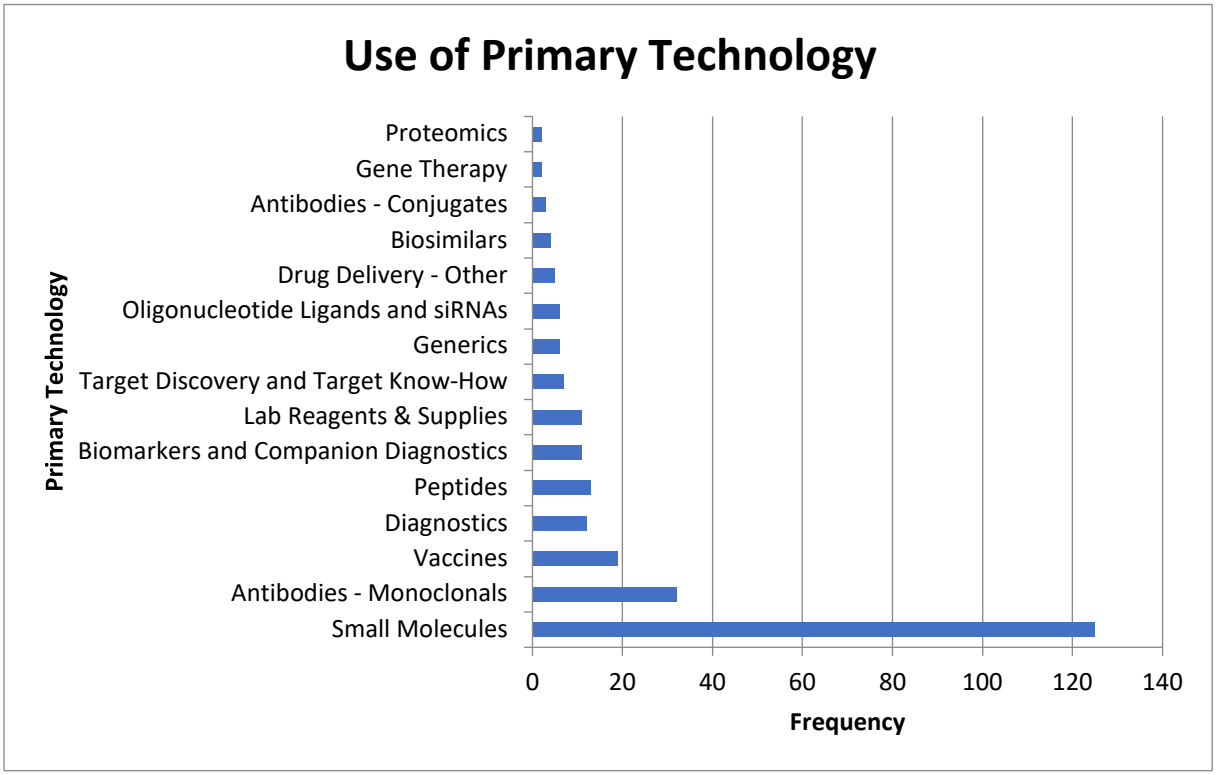

Figure 40: Various primary technologies utilized by Merck.

The majority of transaction deals for Merck occurred during the discovery stage (frequency = 82) and approved phase (frequency = 32), as is shown in Figure 41. Merck considers entering into partnerships with other biotechnology or pharmaceutical companies of great benefit when it comes to identifying new medicine for complicated diseases and thus complement its R&D portfolio. The goal is to create a clinical pipeline that combines internal as well as external sourced assets that are aligned with Merck's strategic goals and fits its PfM. Therefore, the company is looking to balance its portfolios with a mix of licensing technological capabilities at the discovery stage and acquiring products at the approved phase in order to promote the commercialisation of innovate medicine. **[112]**

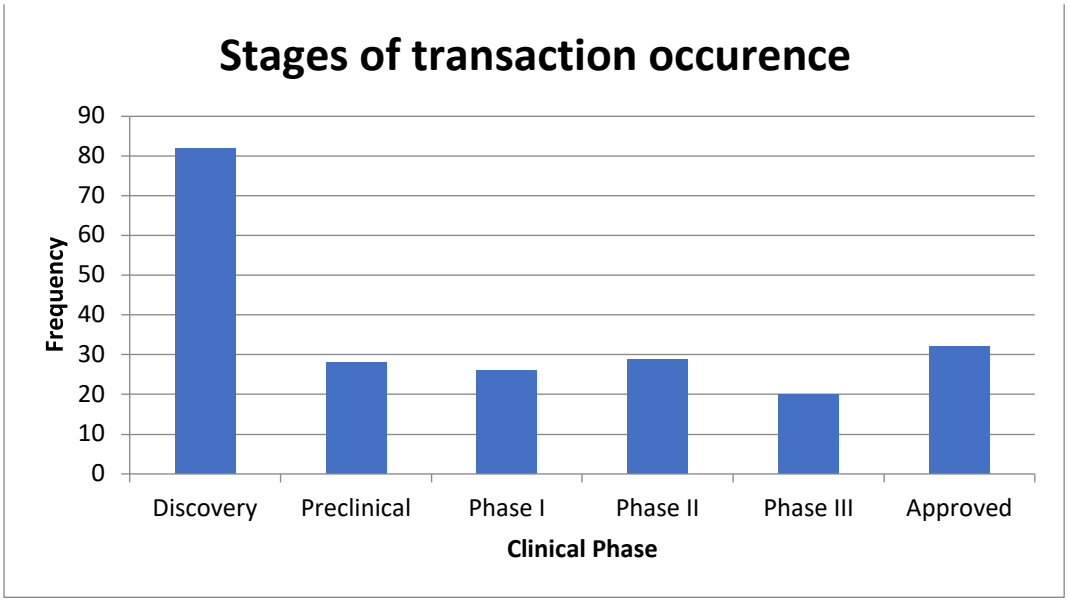

Figure 41: Frequency of transaction deals made by Merck at different clinical stages.

An overview of the size of transaction deals Merck was involved in, is provided in Figure 42, with deals valued over $500 million dollars (frequency = 33) and deals under $50 million dollars (frequency = 28) being the most frequent.

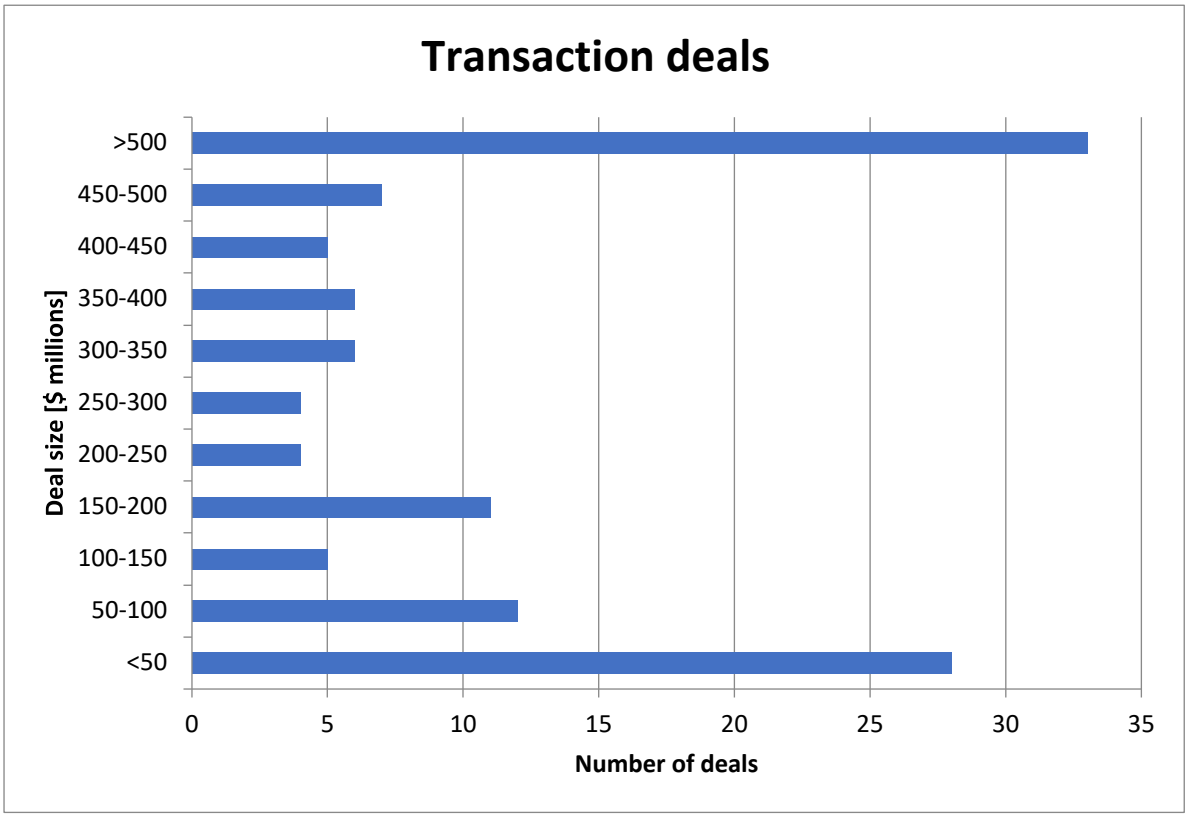

Figure 42: Size and number of transaction deals undertaken by Merck.

Merck entered into an arrangement with F-Star in 2011 for the license rights of modular antibody technology that can be used to find therapeutic methods for inflammatory diseases, as an effort to strengthen its respective portfolio. The deal valued at $690 million dollars also stipulates that Merck will receive exclusive global rights related to the development and commercialisation of any resulting compounds. **[113]**
However, the biggest deal worth approximately $2.3 billion dollars took place when Ablynx and Merck agreed to collaborate on cancer research that could lead to the development of novel cancer medicines formulated on specific antibody fragments, called nanobodies. Merck would be responsible for the further development, production as well as commercialisation of any successful product that stem from the application of the nanobody technology. It was not the only pharmaceutical company that approached Ablynx that has more than seven nanobodies and thirty research programmes either in clinical development or already in its drug pipeline. Abbvie, Novartis and Boehringer Ingelheim are among the top firms that also partnered with Ablynx in order to enhance their cancer portfolio with new medicines. **[114]** One of the lowest transactions of Merck was with OBI Pharmaceuticals, valued at just $3 million dollars regarding the drug Dificid, which is effective against a certain type of diarrhea. Merck would be able to procure exclusive rights to launch the medicine in Taiwan in terms of manufacturing, development and commercialization, thus strengthening its position in the Asian market. **[115]**

Merck has been generally involved with a series of transaction deals with varied values in size as is depicted in Table 12, with most occurring during discovery and approved stages. It follows a risk diversification strategy with its PfM by entering into collaboration with biotechnology companies that specialise in critical disease areas such as cancer, neurology and immunology, and has high interest into expanding its market into new geographies, especially in Asia. **[116]**

Table 12: Size of transaction deals at each clinical stage.

Clinical Stages	Deal Size [$ millions]

Discovery	10	20	68.1	100	150	167	172	200	280
	289	343	350	434	515	595	690	941	2341.4
Preclinical	26.15	41.8	251	450	490.5	702			
Phase I	1.5	7.85	31.6	50	168.5	205.6	375	473	500
	605	1161							
Phase II	12.5	18.6	100	225	325	421	470	574	625.6
	800	1127	1250	2850	3850				
Phase III	6.6	61	136.5	215	290	366.4	452	550	583
	1000								
Approved	0.119	3	6.1	18.44	25	75	367	430	600
	780	2100	9500	14429.8	49600				

Therefore, partnerships, mergers and acquisitions are key elements of its project planning for value creation in the long-term, as it is concentrated in owning innovative technological capabilities or products that can augment its drug pipeline, especially during patent expirations of its blockbusters. Thus, it is focused mainly on procuring products at different stages of the clinical pipeline, from preclinical to Phase III, as is shown in Table 13, while at the discovery stage it prefers to gain access to new clinical technologies like all the previously mentioned pharmaceutical companies and in the approved stage tends to go through the acquisition of companies or business units. All these actions are part of its strategic R&D portfolio management to have as cornerstone highly specialized medicines in diversified projects across many countries that would lead to profitable growth over many years. **[116]**

Table 13: Main asset types during individual clinical phases.

Clinical Stages	Asset Type
Discovery	Technology
Preclinical	Product
Phase I	Product
Phase II	Product
Phase III	Product
Approved	Company/Business Unit

To achieve becoming a leader in the pharmaceutical market and have strong sales as well as margin growth with its major portfolios, Merck aims to expand its existing drug pipelines predominantly through licensing (frequency = 262) and acquire already discovered products (frequency = 156), as illustrated in Figure 43 and 44 respectively. **[116]**

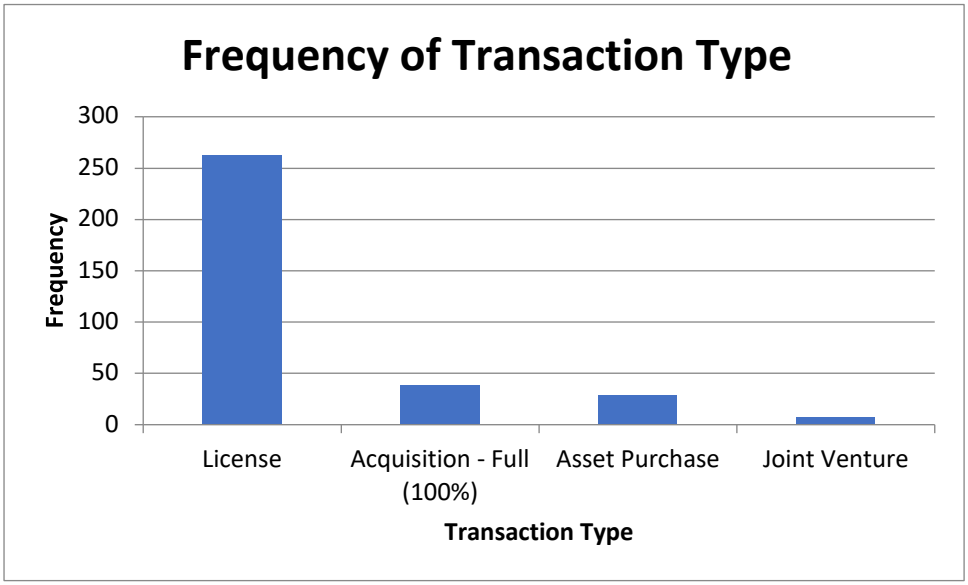

Figure 43: Different types of transactions undertaken by Merck.

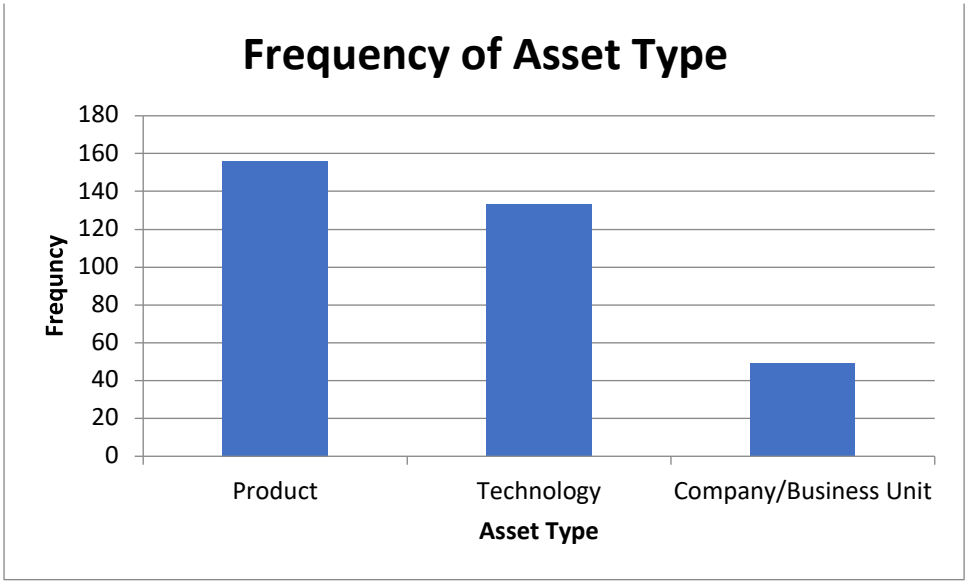

Figure 44: Three main asset types during transactions deals.

Chapter 4 Licensing deals vs internal R&D

Pharmaceutical companies have annually significant R&D expenses for drug discovery and development of critical medicines for a variety of diseases with the dual aim to improve the quality of life of patients and create value for shareholders. The industry as a whole is under

constant pressure from a variety of factors ranging from patent cliff of blockbuster drugs, high attrition rate during clinical trials, high costs and risks to launch a medicine into market. An example can be viewed in Pfizer's annual revenue losses of $11 billion dollars due to Lipitor going off patent in 2011, which composed one sixth of its total 2010 revenues. Therefore, there is common understanding that effective R&D portfolio management is key for long-term growth and profitability. This means that projects within a portfolio should be timely evaluated, undergone through a selection process, accelerated or even prioritized if they show promising results. R&D portfolios are usually organized by therapeutic areas, which encompass different categories of diseases that require specialized research programs in order to attain potential compounds that later could be transformed into commercialized medicine. **[117]**

It is important to note that generally portfolio management can be stratified into portfolio evaluation and portfolio optimization. The former can be represented as the magnitude of the portfolio condition versus risk and value, while the latter incorporates available and optimal selection of strategies to the company that could lead to proficiently accomplishing a needed objective. **[117]**

Therefore, it is perhaps better to discontinue with the present R&D model, which makes it rather complicated to optimize the R&D portfolio and adopt correct strategies that will lead to the right selection of projects. Instead, a combination of internal R&D and external licensing could just prove to be ideal or even fully focusing on licensing deals. For example, GSK abandoned its neurology program completely in 2009 in order to redirect the capital towards external partnerships and projects. However, it is crucial not to fully rely on the know-how and technological capabilities of other companies since it might result to a lower bargaining position and create difficulties in acquisitions of small biotechnology companies or their associated products. Generally speaking, internal and external R&D are paramount in determining a pharmaceutical company's performance and an optimal integration of both would be a key driver for producing innovative medicines as well as have significant ramifications for future growth. **[118]**

External innovation in the form of licensing has experience a surge in the last years among major pharmaceutical companies like Takeda, AstraZeneca and Roche, especially in 2017 approximately 93% of all transaction deals could be related to licensing. There are several reasons behind this, such as the desire to stay competitive, the need of specialized technological platforms to identify interesting compounds faster or to enhance a weakened portfolio with a number of new potentially incipient drug targets. Furthermore, certain therapeutic domains such as neurology and oncology pose substantial challenges in finding new treatments and medicine. As a result, in most cases the licensor is a biotechnology company that focuses on one therapeutic area and has extensive research prowess, experts in the particular field and advanced technologies. This in turn enables pharmaceutical companies to streamline in their key areas of interest where they have robust portfolios, without the need to further incur any additional costs or risks associated with complicated internal projects. **[119]**

Chapter 5 Conclusion and Recommendations

This research has tried to show through a combination of literature review and data analysis of six major biopharmaceutical companies that strategic R&D portfolio management is key factor in their sales revenue, profitability and growth. The most important part of PfM is the selection and prioritization of internal projects that would benefit a firm's drug pipeline and eventually lead to the production of innovative medicine. In addition, it is critical for the long-

term prospects of a company to also focus on choosing the appropriate external projects in collaboration with biotechnology firms that can complement its own R&D portfolio.

The preferred asset type to conduct transaction deals was licensing due to its strategic advantage over merger & acquisitions and joint ventures. A pharmaceutical company does not only gain access to novel technological capabilities for drug discovery and the specialized know-how for the later stages of clinical trials, but also has the opportunity to expand to new geographic regions and thus increase the sale of its products in the new markets. In addition, the financial risk is substantially reduced due to an agreed payment structure, which lowers the burden on its internal R&D expenses. This is also suggested by the data for all six companies.

Furthermore, firms tend to acquire new drug candidates and in some cases business units during the approved phase, while they prefer to license technologies at the discovery stage. The main therapeutic areas for most of them was oncology and neurology, followed by infectious diseases, with most formulated medicine exhibiting inhibit antagonist mechanism of action.

In conclusion, this project managed to showcase certain patterns among six pharmaceutical companies. Of course, a direct comparison between them is not possible due to the lack of complete information about some transaction deals, the difference in the size of the firms and their R&D expenses as well the scope of their overall portfolios. Nevertheless, the companies investigated here, demonstrated that they follow similar patterns in their PfM.

REFERENCES

[1] R. Frank et al, *Pharmaceutical industry profits and research and development*, USCBrookings Schaeffer on Health Policy, **2017**.
[2] A. Schuhmacher et al, *Changing R&D models in research-based pharmaceutical companies*, J. Transl Med., Vol. 14, Issue 105, **2016**.
[3] S. M. Paul et al*, How to improve R&D productivity: the pharmaceutical industry's grand challenge*, Nature Reviews Drug Discovery, Vol. 9, pp. 203-214, **2010**.
[4] F. Pammolli et al, *The productivity crisis in pharmaceutical R&D, Nature Reviews Drug Discovery*, Vol. 10, pp. 428-438, **2011**.

[5] B. Booth et al, *Prospects for productivity*, Nature Reviews Drug Discovery, Vol. 3, pp. 451456, **2004**.
[6] B. Munos, *Lessons from 60 years of pharmaceutical innovation*, Nature Reviews Drug Discovery, Vol. 8, pp. 959-968, **2009**.
[7] DiMassi, *Risks in new drug development: approval success rates for investigational drugs*, Clinical Pharmacology&Therapeutics, Vol. 69, No. 5, pp. 297-307, **2001**.
[8] RG Cooper et al, *Portfolio Management-Fundamental to New Product Success*, Working Paper No.12, **2001**.
[9] Mathur, S., *Project portfolio management techniques*, PMI® Global Congress 2006—Asia Pacific, Bangkok, Thailand, Newtown Square, PA: Project Management Institute, **2006**. **[10]** M. Hartmann et al, *Application of real options analysis for pharmaceutical R&D project valuations-Empirical results from a survey*, Research Policy, Vol. 35, Issue 3, **2006**. **[11]** P. Breeze et al, *Valuing Trial Designs from a Pharmaceutical Perspective Using ValueBased Pricing*, Health Economics, Vol. 24, Issue 11, **2014**.
[12] Catrina M. Jones, *Managing Pharmaceutical Research And Development Portfolios: An Empirical Inquiry Into Managerial Decision Making In The Context of a Merger*, Georgia State University, **2016**.
[13] Michael M. Menke, *Making R&D Portfolio Management More Effective*, Journal of Research-Technology Management, Vol. 56, Issue 5, **2013**.
[14] R.F. Tiggemann et al, *Project Portfolio Management: A powerful strategic weapon in pharmaceutical development*, Drug Information Journal, Vol. 32, Issue 3, **1998**.
[15] P. Breeze, *Valuing trial designs from a pharmaceutical perspective using value-based pricing*, Health Economics, Vol. 24, Issue 11, **2014**.
[16] L. Kester et al, *Exploring portfolio decision-making processes*, Journal of Product Innovation Management, Vol. 28, Issue 5, **2011**.
[17] D. Grainger, *D&D On R&D - Lessons For Pharma From The Dungeon Master*, Forbes, **2014**.
[18] D. Smith et al, *From Budget-Based to Strategy-Based Portfolio Management: A Six-Year Case Study*, Research-Technology Management, Vol. 56, Issu 5, pp. 45-51, **2013**. **[19]** Bode-Greuel, K. M et al, *Value-driven project and portfolio management in the pharmaceutical industry: Drug discovery versus drug development–Commonalities and differences in portfolio management practice*, Journal of Commercial Biotechnology, Vol. 14, Issue 4, pp. 307-325, **2008**.
[20] Evans, R., *Portfolio analysis and R&D decision making*, Nature Reviews Drug Discovery, Vol. 8, Issue 3, pp. 189-190, **2009**.
[21] J. A. DiMasi et al, *The price of innovation: New estimates of drug development costs*, Journal of Health Economics, Vol. 22, Issue 2, pp. 151-85, **2003**.
[22] D.Rodriguez, *Decisions of Pharmaceutical Firms for New Product Development*, MIT Industrial Performance Working Paper, **1998**.
[23] C. Chapman, *Project Risk Management: Processes*, Techniques and Insights, Rexdale, Ontario: Wiley, **1996**.
[24] V. Krishnan et al, *Product Development Decisions: A Review of the Literature*, Management Science, 47(1):1–21. **2001**.
[25] K. L. Poh et al, *A Comparative Evaluation of R&D and Project Evaluation Methods*, R&D Management, Vol. 31, Issue 1, pp. 63–75, **2001**.
[26] N. French et al, *Discounted cash flow: accounting for uncertainty*, Journal of Property Investment & Finance, Vol. 23, Issue 1, **2005**.

[27] J. D. Linton et al, *Analysis, Ranking, and Selection of R&D Projects in a Portfolio*, R&D Management, Vol. 32, Issue 2, pp. 139–148, **2002**. **[28]** G. Morgan, *Uncertainty: A Guide to Dealing*
with Uncertainty in Quantitative Risk and Policy Analysis, Cambridge, UK: Cambridge University Press, **1990**.
[29] H. M. Markowitz, Portfolio Selection, 2d ed. Cambridge, MA: Blackwell Publishers, **1991**.
[30] T. Sharpe et al, *How Smithkline-Beecham Makes Better Resource Allocation Decisions*, Harvard Business Review (March–April):45–57, **1998**.
[31] M. Ding et al, *Structuring the New Product Development Pipeline*, Management Science, Vol. 48, Issue 3, pp. 343–363, **2002**.
[32] T. C. Copeland et al, *Real Options: A Practitioner's Guide*, New York: Texere Publishing Limited, **2001**.
[33] M. Amram et al, *Real Options: Managing Strategic Investment in an Uncertain World*, Boston, MA: Harvard Business School Press, **1999**.
[34] A. Banerjee, *Real Option Valuation of a Pharmaceutical Company*, The Journal for Decision Makers, Vol. 28, Issue 2, **2003**.
[35] C. H. Loch et al, *Evaluating Growth Options as Sources of Value for Pharmaceutical Research Projects*, R&D Management, Vol. 31, Issue 2, pp. 231–243, **2001**.
[36] P. O'Connor*, Implementing a Stage-Gate Process: A Multi-Company Perspective*, Journal of Product Innovation Management, Vol. 11, Issue 3, pp. 183–200, **1994**.
[37] P. H. Andersen et al, *Inter-partner learning in global supply chains: lessons from Novo Nordisk*, European Journal of Purchasing & Supply Management, Vol. 6, Issue 2, pp. 105-116, **2000**.
[38] L. Kester et al, *Portfolio decision-making genres: A case study*, Journal of Engineering and Technology Management, Vol. 26, Issue 4, pp. 327-341, **2009**.
[39] Novo Nordisk, https://www.novonordisk.com/research-and-development/our-therapyareas.html, **2020**.
[40] C. Mostrup, Novo Nordisk, https://novonordiskfonden.dk/en/news/dkk-250-millionallocated-for-research-on-endocrine-and-metabolic-diseases/, **2020**.
[41] M. Marre at al, *GLP-1 receptor agonists today*, Diabetes Research and Clinical Practice, Vol. 93, Issue 3, pp. 317-327, **2011**.
[42] D. Isaacs et al, Role of glucagon-like peptide 1 receptor agonists in management of obesity, AJHP, Vol. 73, Issue 19, pp. 1493-1507, **2016**.
[43] M. J. Romero et al, *Role of growth hormone-releasing hormone in dyslipidemia associated with experimental type 1 diabetes*, PNAS, Vol. 113, Issue 7, pp. 1895-1900, **2016**.
[44] *Genmab Licenses DuoBody Platform to Novo Nordisk*, GenEng News, https://www.genengnews.com/topics/drug-discovery/genmab-licenses-duobody-platformto-novo-nordisk/, **2015**.
[45] A. Hidalgo, *Novo A/S acquires Xellia Pharmaceuticals*, Nordic Life Sciences, https://nordiclifescience.org/novo-as-acquires-xellia-pharma-pharmaceuticals/ **2013**. **[46]** J. Levin, *Caisson Biotech enters into development and License agreement with Novo Nordisk*, Fierce Biotech, https://www.fiercebiotech.com/biotech/caisson-biotech-entersinto-development-and-license-agreement-novo-nordisk, **2012**.
[47] Novo Nordisk, Annual report 2019, https://www.novonordisk.com/content/dam/Denmark/HQ/investors/irmaterial/annual_report/2020/Novo-Nordisk-Annual-Report-2019.pdf, **2019**.

[48] Boehringer Ingelheim, *Boehringer Ingelheim Annual Report 2019*, https://annualreport.boehringeringelheim.com/fileadmin/PDF/EN/BI_Finanzbericht_2019_en.pdf, **2019.**

[49] Boehringer Ingelheim, Pipeline Strategies, https://www.inoncology.com/pipelinestrategies, **2020**.

[50] Boehringer Ingelheim, *Cancer Immunology Research at Boehringer Ingelheim,* https://www.boehringer-ingelheim.com/therapeutic-areas/cancer-immunology/cancerimmunology-research, **2020**.

[51] Boehringer Ingelheim, *Metabolic Diseases*, https://www.boehringeringelheim.in/metabolic-diseases/diabetes, **2020**.

[52] Boehringer Ingelheim, *Boehringer Ingelheim intensifies CNS research with two new partnerships*, https://www.boehringer-ingelheim.us/sites/us/files/partnering_content_card_images/edition_3_june_2014_final.pdf, **2014**.

[53] Boehringer Ingelheim, *Boehringer Ingelheim and OSE immunotherapeutics announce global immuno-oncology partnership to develop a pioneering checkpoint inhibitor for the treatment of advanced solid tumors*, **2020**.

[54] L. Bhatt et al, *Recent advances in clinical development of leukotriene B4 pathway drugs*, Seminars in Immunology, Vol. 33, pp. 65-73, **2017**.

[55] Boehringer Ingelheim, *Innovation in Oncology and Cancer Immunology Research*, https://www.boehringer-ingelheim.com/human-pharma/innovation-diseasefocus/oncology-and-cancer-immunology-research, **2020**.

[56] T. Urbankova, *Boehringer Ingelheim breaks ground on its strategic vaccine production center for veterinary public health*, https://www.boehringer-ingelheim-hr.ml/pressrelease/groundbeaking-vaccine-production-center-france, **2019**.

[57] Hikma Press Release, https://www.hikma.com/newsroom/article-i2284-hikmaacquires-roxane-laboratories-transforming-its-position-in-the-us-generics-market/, **2015**.

[58] The Economist Intelligence Unit, *Sanofi, Boehringer Ingelheim agree to asset swap*, Healthcare, http://www.eiu.com/industry/article/1384361322/sanofi-boehringeringelheim-agree-to-asset-swap/2016-06-28 **2016**.

[59] L. Timmerman, *Forma Cuts $64 M deal with Boehringer Ingelheim to discover cancer drugs*, Xconomy, https://xconomy.com/boston/2012/01/05/forma-cuts-65m-deal-withboehringer-ingelheim-to-discover-cancer-drugs/, **2012**.

[60] Press Release, *Exelixis and Boehringer Ingelheim Enter into collaboration for development of S1P1 Receptor Agonists in the Field of Autoimmune diseases*, https://ir.exelixis.com/news-releases/news-release-details/exelixis-and-boehringeringelheim-enter-collaboration, **2009**.

[61] J. Levin, Boehringer Ingelheim and Funxional Therapeutics announce acquisition of Funxional's FX125L and the somatotaxin portfolio to treat inflammation, https://www.fiercebiotech.com/biotech/boehringer-ingelheim-and-funxional-therapeuticsannounce-acquisition-of-funxional-s-fx125l, **2012**.

[62] Boehringer Ingelheim, *Our human pharma research and development pipeline*, https://www.boehringer-ingelheim.com/research-development/pipeline/research-anddevelopment-pipeline?, **2020**.

[63] Takeda, *Company Information*, https://www.takeda.com/who-we-are/companyinformation/, **2020**.

[64] Takeda, *Corporate Overview 2020*, https://www.takeda.com/4a34db/siteassets/system/newsroom/corporate materials/takeda-corporate-overview_english_aug_2020_1.pdf, **2020**. **[65]**

I. Petrakis, *Strategic agreements for Takeda's portfolio in Oncology and Gastroenterology*, https://www.takeda.com/bg-bg/newsroom/newsreleases/2017/strategic-agreements-for-takedas-portfolio-in-oncology-andgastroenterology/, **2017**.

[66] A. Plump, *Focused World Class R&D*, Takeda, https://www.takeda.com/siteassets/system/investors/report/quarterlyannouncements/fy2016/takeda-ir-day-held-on-june-9-2016/2.-focused-world-class-rd.pdf, **2016**.

[67] Takeda, *Rare Diseases*, https://www.takeda.com/what-we-do/areas-of-focus/rarediseases/, **2020**.

[68] Takeda, *Platform Technology (new modalities and drug delivery systems)*, https://www.takeda.com/en-au/what-we-do/research--development/cockpit/platform02/, **2020**.

[69] Takeda, *Takeda licenses rights to use ImmunoGen*, Inc's novel antibody-drug conjugate technology, https://www.takeda.com/newsroom/newsreleases/2015/takeda-licensesrights-to-use-immunogen-inc.s-novel-antibody-drug-conjugate-technology/, **2015**.

[70] Takeda, *Takeda Research & Development Fact Sheet*, https://www.takeda.com/4a4224/siteassets/system/what-we-do/research-anddevelopment-rd-in-takeda/takeda-rd-fact-sheet_final.pdf, **2020**.

[71] J. Topham et al, *Takeda to buy Swiss drugmaker Nycomed for $13.7 billion*, Reuters, https://www.reuters.com/article/us-takeda-nycomed/takeda-to-buy-swiss-drugmakernycomed-for-13-6-billion-idUSTRE74I15620110519, **2011**.

[72] E. Gibbs, *Takeda to buy Millenium Pharma for $8.8 billion*, Business News, Reuters, https://www.reuters.com/article/us-millennium-idUST18218420080410, **2008**. **[73]** S. Elvidge, *Takeda terminates MacroGenics DART deal early*, Biopharma Dive, https://www.biopharmadive.com/news/takeda-terminates-macrogenics-dart-dealearly/426186/, **2016**.

[74] Takeda, *Corporate Philosophy*, https://www.takeda.com/who-we-are/corporatephilosophy/#:~:text=and%20Strategic%20Roadmap.-,Mission,through%20leading%20innovation%20in%20medicine., **2020**.

[75] AstraZeneca, *Our Company*, https://www.astrazeneca.com/our-company.html, **2020**. **[76]** AstraZeneca, *Key Facts*, https://www.astrazeneca.com/investor-relations/key-facts.html, **2020**.

[77] AstraZeneca, *Oncology,* https://openinnovation.astrazeneca.com/about-us/our-rndfocus-areas.html#oncology, **2020**.

[78] AstraZeneca, *Infection and Vaccines*, https://www.astrazeneca.com/our-therapyareas/infection-and-vaccines.html, **2020**.

[79] M. Molteni et al, *Natural products with toll-like receptor 4 antagonist activity*, International Journal of Inflammation, Article ID 2859135, **2018**.

[80] E. J. Mifsud et al, *TLR agonists as modulators of the innate immune response and their potential as agents against infectious disease*, Front. Immunol., **2014**. **[81]** AstraZeneca, *Metabolism*, https://www.astrazeneca.com/our-therapyareas/cardiovascular-renal-and-metabolism/metabolism.html, **2020**.

[82] AstraZeneca, *Drug Modalities*, https://www.astrazeneca.com/what-science-cando/drug-modalities.html, **2020**.

[83] AstraZeneca, *AstraZeneca recognised as pharma's 'top dealmaker'*, https://www.astrazeneca.com/media-centre/articles/2019/astrazeneca-recognised-aspharmas-top-dealmaker-20082019.html, **2019**.

[84] AstraZeneca, *AstraZeneca and Isis Pharmaceuticals to discover and develop antisense drugs for cardiovascular, metabolic and renal diseases*, Pharmaceutical Technology, https://www.astrazeneca.com/media-centre/press-releases/2015/astrazeneca-isispharmaceuticals-antisense-drugs-cardiovascular-metabolic-renal-diseases-03082015.html#, **2015**.

[85] Pharma Letter Authors, *AstraZeneca aligns with Regulus for microRNA therapeutics*, ThePharmaLetter, https://www.thepharmaletter.com/article/astrazeneca-aligns-withregulus-for-microrna-therapeutics, **2012**.

[86] A. Pollack, *AstraZeneca Buys MedImmune for $15.6*, The New York Times, https://www.nytimes.com/2007/04/24/business/24drug-web.html, **2007**.

[87] S. Sutton, *Bicycle Therapeutics Announces Broad Partnership with AstraZeneca to Develop Bicyclic Peptides*, BusinessWire-A Berkshire Hathaway company, https://www.businesswire.com/news/home/20161201005108/en/Bicycle-TherapeuticsAnnounces-Broad-Partnership-AstraZeneca-Develop **2016**.

[88] A. Keown, *Pharma Giant AstraZeneca PLC in Advanced Talks to Buy Acerta Pharma for $5 billion*, BioSpace, https://www.biospace.com/article/pharma-giant-astrazeneca-plc-inadvanced-talks-to-buy-acerta-pharma-for-5-billion-/, **2015**. **[89]** J. Gardner, *Pharma of the Year: AstraZeneca*, Biopharma Dive, https://www.biopharmadive.com/news/astrazeneca-pharma-dive-awards/566229/, **2019**.

[90] Roche, *Get to know Roche in brief*, https://www.roche.com/about.htm, **2020**.

[91] Roche, *Our Response to cancer always starts with the science*, https://www.roche.com/research_and_development/what_we_are_working_on/oncology/leading-science.htm, **2020**.

[92] Roche, *The immense challenges of neuroscience*, https://www.roche.com/research_and_development/what_we_are_working_on/neuroscience/rare-diseases-challenges.htm, **2020**.

[93] Roche, *New Roche data at the 2019 AAN Annual Meeting showcase breadth and promise of neuroscience portfolio*, https://www.roche.com/media/releases/med-cor-201904-29.htm, Basel, **2019**.

[94] Roche, *About infectious diseases*, https://www.roche.com/research_and_development/what_we_are_working_on/infectious_diseases/about_infectious_diseases.htm, **2020**.

[95] J. A. Flygare et al, *Discovery of a potent small-molecule antagonist of inhibitor of apoptosis (IAP) proteins and clinical candidate for the treatment of cancer (GDC-0152)*, J. Med. Chem., Vol. 55, Issue 9, pp. 4101-4113, **2012**.

[96] C. Ullmer et al, *Functional monoclonal antibody acts as a biased agonist by inducing internatlization of metabotropic glutamate receptor 7*, Br J. Pharmacol, Vol. 167, Issue 7, pp. 1448-66, **2012**.

[97] Roche, *About Oncology*, https://www.roche.com/research_and_development/what_we_are_working_on/oncology/about_oncology.htm, **2020**.

[98] Roche, *Roche to restructure its manufacturing network for small molecules*, https://www.roche.com/media/releases/med-cor-2015-11-12.htm, **2015**. **[99]** Trefis Team, *Roche sees small molecule opportunity differently now, Forbes*, https://www.forbes.com/sites/greatspeculations/2015/11/13/roche-sees-small-moleculeopportunity-differently-now/#1b833f6d4230, **2015**.

[100] Roche, *Our Business Priorities*, https://www.roche.com/about/priorities.htm, **2020**.

[101] Authors, *Roche to pay aileron $25M to tap into stapled peptide expertise*, Genetic Engineering & Biotechnology News, https://www.genengnews.com/topics/drugdiscovery/roche-to-pay-aileron-25m-to-tap-into-stapled-peptide-expertise/, **2010**. **[102]** PTC Therapeutics, *PTC Therapeutics announces drug discovery collaboration with Roche*, https://www.drugdiscoveryonline.com/doc/ptc-therapeutics-announces-drugdiscovery-0001, **2009**.

[103] S. Kuber, *ImmunoCellular in research and license option deal with Roche*, Reuters Biotechnology, https://www.reuters.com/article/immunocellular/immunocellular-inresearch-and-license-option-deal-with-roche-idUSBNG53242920090909, **2009**. **[104]** M. Fitzhugh, *Roche to acquire Santaris Pharma for up to $450M*, BioWorld, https://www.bioworld.com/articles/366025-roche-to-acquire-santaris-pharma-for-up-to450m, **2014**.

[105] Roche, *This is personalised healthcare*, https://www.roche.com/about/priorities/personalised_healthcare.htm, **2020**.

[106] Merck, *Who we are*, https://www.merckgroup.com/en/company/who-we-are.html, **2020**.

[107] Merck, *Strategy & Values*, https://www.merckgroup.com/en/company/who-weare/strategy-and-values.html#:~:text=Our%20strategy%20is%20based%20on,%E2%80%9D%20and%20%E2%80%9CBroad%20Minds%E2%80%9D., **2020**

[108] Merck, *Oncology*, https://www.merckgroup.com/en/expertise/oncology.html, **2020**.

[109] Merck, *Infectious diseases*, https://www.merck.com/research-andproducts/infectious-diseases/, **2020**.

[110] Merck, *Merck's commitment to addressing infectious diseases*, https://www.merck.com/docs/Merck-Commitment-to-ID-Infographic-AINF-1212457-0000Final.pdf, **2020**.

[111] L. M. Jarvis, *Merck to acquire oncology-focused small-molecule firm ArQule*, C& EN, https://cen.acs.org/articles/97/web/2019/12/Merck-acquire-oncology-focused-small.html, **2019**.

[112] Merck, *Strategic focus & partnerships*, https://www.merckgroup.com/en/company/partnering/collaboration/collaboration-inhealthcare/strategic-focus-and-partnerships.html, **2020**.

[113] K. FitzGerald, *F-Star and Merck Serono to collaborate in the discovery and development of novel targeted biologics*, http://www.f-star.com/media/60185/-20110907F-Star-and-Merck-Serono-to-collaborate-in-the-discovery-and-development-of-noveltargeted-biologics.pdf, **2011**.

[114] Authors, *Ablynx, Merck launch up to $2.3 B cancer collaboration*, Genetic Engineering & Biotechnology News, https://www.genengnews.com/news/ablynx-merck-launch-up-to-23b-cancer-collaboration/, **2014**.

[115] S. Lee, *OBI Pharmaceuticals enters exclusive agreement with MSD for rights to DIFICID (fidaxomicin) in Taiwan*, https://www.biospace.com/article/releases/obi-pharmaceuticalsenters-exclusive-agreement-with-b-msd-b-for-rights-to-dificid-fidaxomicin-intaiwan-/, **2015**. **[116]** Merck, *Strategy*, https://www.merckgroup.com/en/annualreport/2019/combinedmanagement-report/fundamental-information-about-the-group/strategy.html, **2019**. **[117]** M. Ding et al, *Portfolio Management in New Drug Development*, Chapter 3: Innovation and Marketing in the Pharmaceutical Industry, **2014**.

[118] M. Ceccagnoli et al, *Internal R&D versus in-licensing complements or substitutes*, Georgia Institute of Technology, Denmark, **2012**.
[119] P. Pfrang et al, *External innovation-How biopharma companies are bolstering R&D pipeline through deal making*, Deloitte, https://www2.deloitte.com/us/en/insights/industry/health-care/biopharma-companiesdeals-research-development.html, **2017**.