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Attribute Analysis of Pipeline Molecules

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CERTIFICATE

This is to certify that Dr. Juhi Harjai has undergone her summer training in IMS Health, Gurgaon from 7th April, 2014 to 6th June, 2014.The candidate herself carried out all the studies related to her summer training. Her approach to the study has been scientific and analytical. This summer training is partial fulfilment of course requirement is recommended for the award of post graduate diploma in hospital management.

I wish her success in all her future endeavours.

Dr. Ashok Kaushik

Dean(Academic & Student Affairs)

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To Whom So Ever it May Concern

This is to certify that **Dr. Juhi Harjai**, a student of the Post Graduate Diploma in Hospital and Health Management, IIHMR Jaipur has worked under our guidance and supervision. This Summer Project Report on '**Attribute Analysis of Pipeline Molecules'** has the requisite standard and to the best of our knowledge no part of it has been reproduced from any other summer project, monograph, report or book

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I hope that I can build upon the experience and knowledge that I have gained and make a valuable contribution towards the industry in coming future.

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INTRODUCTION

Company profile:

IMS Health is the world's leading information, services and technology company dedicated to making healthcare perform better.

By applying cutting-edge analytics and proprietary application suites hosted on the IMS one intelligent cloud, the company connects more than 10 petabytes of complex healthcare data on diseases, treatments, costs and outcomes to enable our clients to run their operations more efficiently.

Drawing on information from 100,000 suppliers and on insights from more than 45+ billion healthcare transactions processed annually, IMS Health's approximately 10,000 professionals drive results for over 5,000 healthcare clients globally.

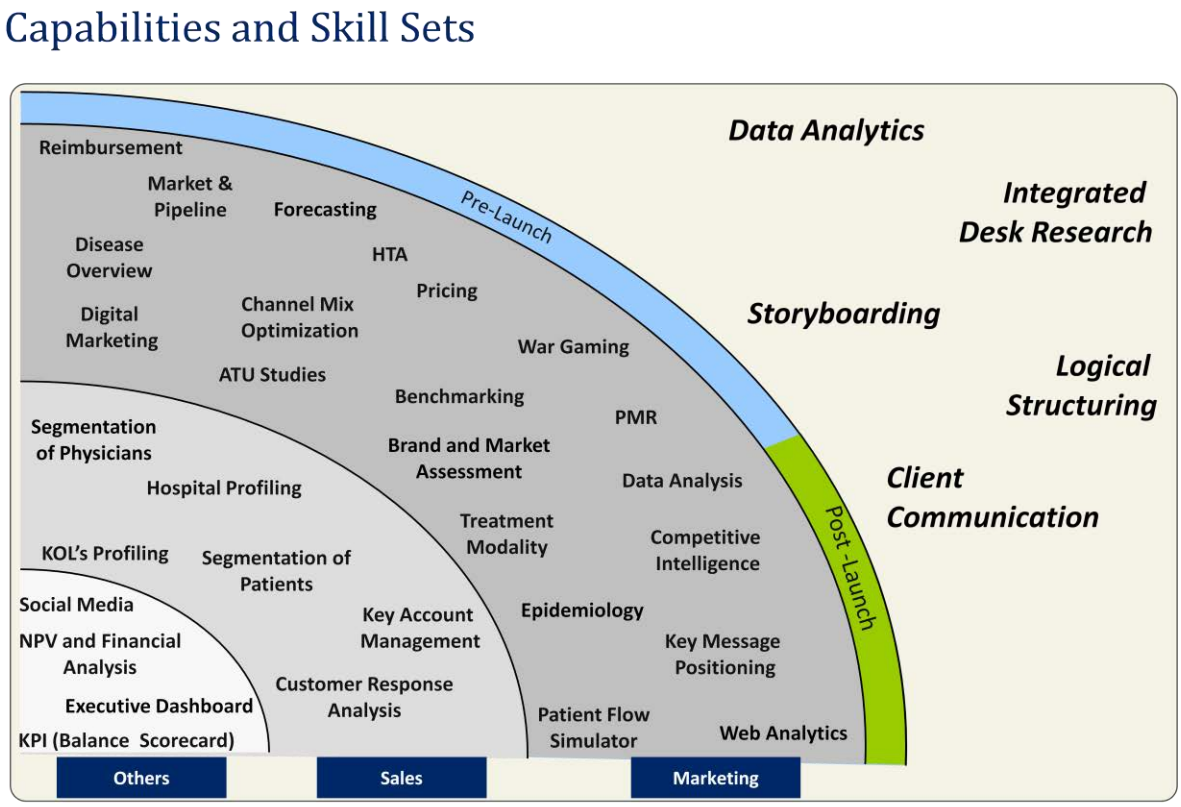
Customers include pharmaceutical, medical device and consumer health manufacturers and distributors, providers, payers, government agencies, policymakers, researchers and the financial community.

The company is having unique vantage point, unmatched scale, expertise and resources to connect the dots for clients and make healthcare perform better at **IMS Health India Private Limited Global Offshore Center, Gurgaon**.

I got the opportunity to work in Market Assessment team (**Figure 1**) and assisted in many projects like:

1. Attribute Analysis of Pipeline Molecules
2. Secondary desk research for Product launch by a healthcare company in a particular country
3. Qualitative data –Sales analysis of drugs in a particular country-Qualitative data analysis
4. Country landscape project-for all countries-secondary desk research and qualitative data analysis

Figure 1: An overview of Market Assessment Team



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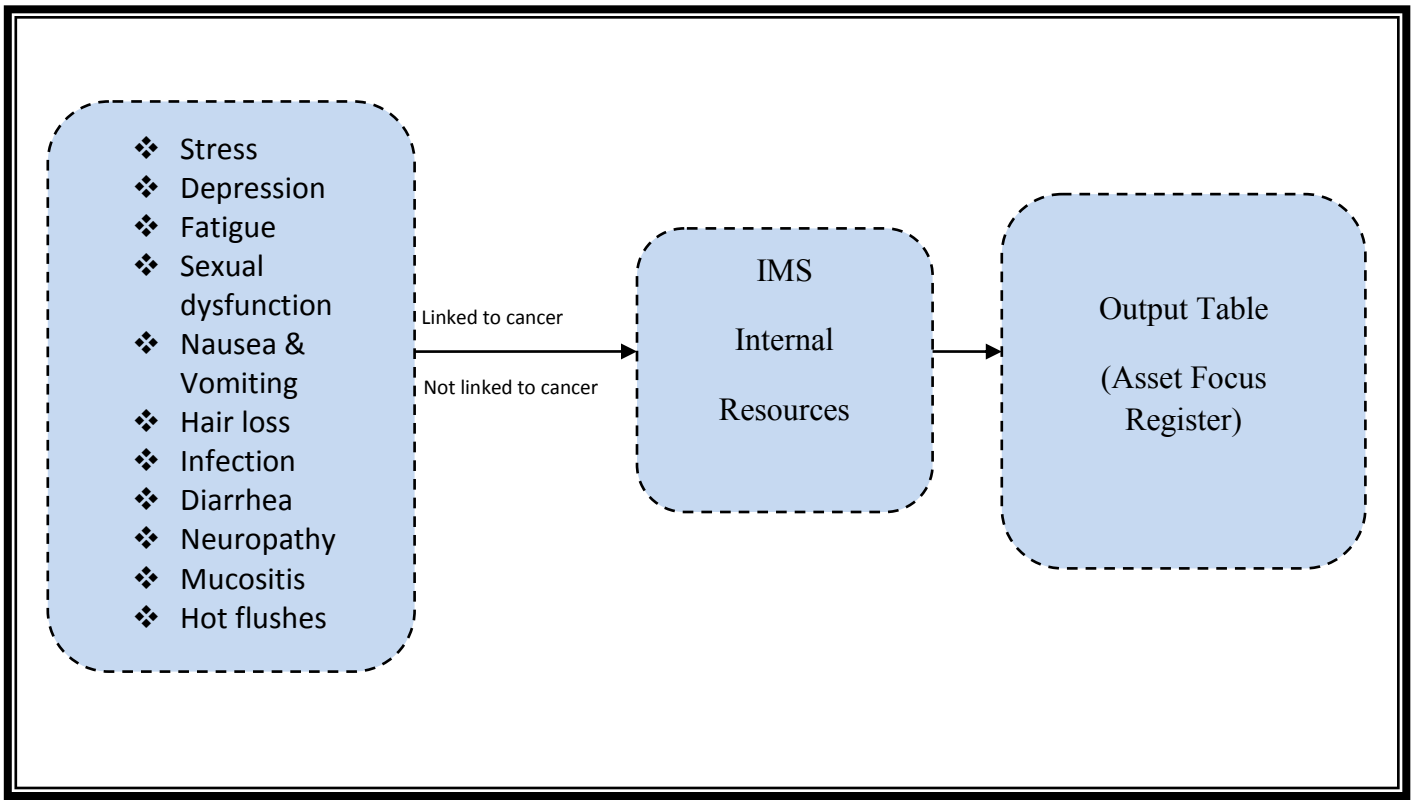
The **healthcare company** associated with the project wanted to get active products database from IMS. They were interested in the indication; specifically linked to cancer across different countries. Company required an excel spread sheet with certain following parameters like molecule / active ingredient, Phase (preclinical through to phase iii),Indication / side effect (from the list below in **Table 1**), Indication / side effect linked to cancer (is the molecule in development indicated for the side effect in general or is it specifically for the side effect linked to cancer. The action points were formed and information was collected from: IMS internal sources (R& D focus)- which was the main source of database for this project, European trial register, WHO and Company websites. Research was conducted for products in active development for 11 indications. The scheme for identification of molecules of interest considered is explained (**Figure 2)**.

Table 1: Indications for which active molecules needs to be searched

Indications
Stress
Fatigue
Depression
Hot flushes
Sexual dysfunction
Nausea and vomiting
Hair loss
Infection
Diarrhea
Neuropathy
Mucositis

Figure 2: Scheme for identification of molecules of Interest



Overview of the project:

- **Geographical scope**-Global
- **Data sources used-**
  - IMS Internal Resources
  - Company websites
  - European trial register
  - WHO
- **Parameters considered-**
  - Molecule
  - Phase
  - Indication/side effect linked to cancer
  - Indication / side effects linked to cancer
- **Inclusion criteria-**
  - Currently active trials in focused indications will be included on the Asset Database.
  - Molecules related to or not linked to the cancer were included
- **Exclusion criteria** –
  - Removed molecules in phases: discovered, discontinued, suspended, withdrawn and marketed.
  - Vaccines
- **Screening process involved criteria** like:
  - Urgency
  - Development risk
  - Cancer indication
  - Indications
  - Company type
  - Ownership

RATIONALE

The purpose of taking up this project was getting the opportunity to explore a new field of work.

Work done included:

• Screened database for potential assets - Healthcare company wanted the Asset register database of pipeline products created and screened in order to create a focused list of candidate assets

• Molecules filtered by Trial Phase - Screening should help to identify the product development risk (novel/me-too/augmented/extension).

• Less focused indication like molecules with higher unmet needs would be highlighted so that they can be worked upon as they are expected to be the most attractive to the client.

• Screening would help to identify whether the product is being developed in relation to cancer/chemotherapy or not.

REVIEW OF LITERATURE

Pipeline molecules

In the pharmaceuticals sector, a drugs pipeline consists of the drugs that a company has under development or is testing. This includes completely new drugs, variants of existing drugs and new applications of existing drugs.

The pipeline starts with new drug discoveries and it is important to assess companies' ability to discover new drugs as well as drugs that are currently in the pipeline. The early stage of the pipeline needs to be refilled as drugs move up. Good R & D is crucial. [1]

Research pipeline

Drug Discovery

The true process of drug discovery begins after the validation has been completed. Medicinal chemists like Dr. Brown, who understand the nature of molecules from the perspective of chemistry and also understand the role of different molecules in the human body, develop small molecules that stop the target protein from causing the disease.

There are a few important characteristics that a molecule must have to be considered for drug development:

- It must be selective in the way it interacts with proteins to ensure that it only acts on the disease protein
- It cannot be toxic
- It must be distributed in the body in a way that ensures it reaches the disease site, it needs to be easily manufactured
- It needs to be something that no-one has discovered – or more importantly, patented – before.

Drug discovery experts use three different approaches to find a small molecule that will serve as an effective drug: physical screening, virtual screening, and by protein structure based design.

Physical screening

To physically screen small molecules against a disease target protein, chemists use known databases of small molecules that have already been identified and are often patented. In plates that have 96 wells, the target protein is loaded into each well in micro scale amounts and a different small molecule is added to each one. When the chemist finds one that reacts, often seen through a change in the color of the liquid in the well, he or she can then modify it into a new molecule that has a more potent effect on the target.

Virtual screening

By knowing the molecular structure of the target protein, which often takes years of work by basic scientists, chemists can compare the structure of the protein to models of the structure of small molecules. This allows the scientists to rapidly and cost-effectively screen the target against a potentially infinite library of molecules. Once several potential matches have been found using the modeling software, the small molecules will be physically tested for their potential to react with the target protein.

Structure-based design

Chemists can also specifically design small molecules to fit into the known physical properties of the target protein. Using software that can identify the important properties that need to be matched – such as volume, charge, steric constraints, and hydrogen-bonding ability – chemists can discover the precise reciprocal properties needed in the drug molecule. After that, it is a matter of creating this molecule with the same techniques that students learn in organic chemistry labs.

Once several likely candidates have been identified through one of these processes, medicinal chemists not only perform studies to ensure that the protein and drug interact correctly in a test tube, but also in tissue cultures. This is important because the drug must act within the context of a cell, which is a much more complicated environment than a sterile test tube in a lab.

Translational Studies

The next stage in the Research Pipeline carries the small molecule from the drug discovery identification stage and prepares it as a drug, ensuring the molecule interacts is also effective within the infinitely more complex environment of the body. Using preclinical models, scientists study whether the potential new drug arrives at the target cells in the appropriate tissue, reaches this target before it is removed from the body (through the urine or by metabolism), and does act to stop the disease process. One of the other important considerations is the toxicity of the drug to other tissues. Before a trial can begin in the clinic, scientists must prove that the new drug is safe.

Clinical Trials

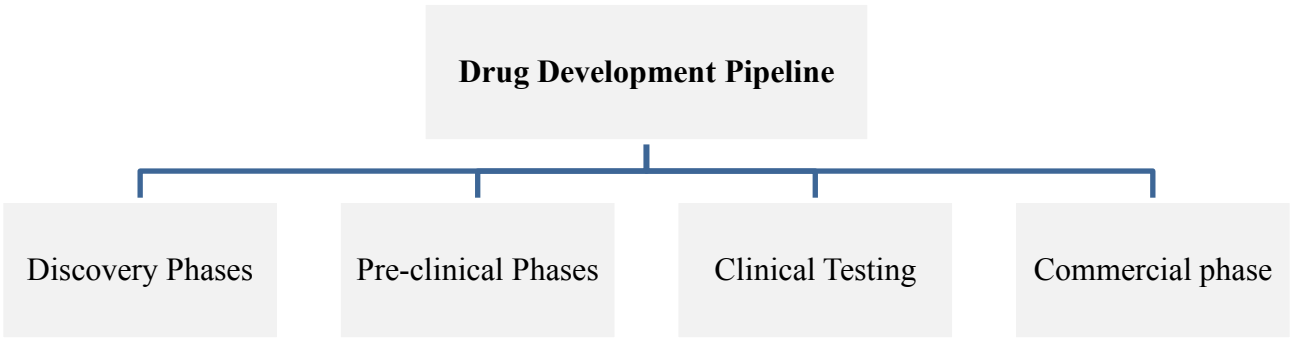
Phase 0 trials study the distribution of the drug in the human body. Using non-therapeutic doses that are tagged with radiolabels, doctors will be able to view where the drug is delivered within the body using applications such as PET imaging. This will enhance the Phase 1 process because physicians will already know where in the body the drug is acting.

Phase 1 trials establish the safety of the drug for humans. Before these trials can take place, investigators must submit an Investigational New Drug application to the Food and Drug Administration to receive permission to run the trial. Looking at potential short-term toxicities, patients in Phase 1 trials are the first to receive therapeutic doses of the drug. In cancer clinical care, these trials often offer patients the only treatment option for advanced disease.

Phase 2 and 3 trials focus on the effectiveness of the drug. Typically, these are large trials conducted in partnership with industry. Phase 2 trials are specific to identifying the appropriate dose for patients, while Phase 3 examines the drug's efficacy in treating the disease and its short-term effects on the patient. Industry most often joins the drug discovery and development process at the Phase 2 stage when synthesis of the drug needs to be scaled up to provide enough of the molecule for the trials.

After the completion of Phase 3 trials, information about all of the trials is submitted to the Food and Drug Administration for approval. [2]

Figure 3: Therapeutic Drug Discovery Pipeline [3]



Principles of early drug discovery: -

Developing a new drug from original idea to the launch of a finished product is a complex process which can take 12–15 years and cost in excess of $1 billion. The idea for a target can come from a variety of sources including academic and clinical research and from the commercial sector. It may take many years to build up a body of supporting evidence before selecting a target for a costly drug discovery program. Once a target has been chosen, the pharmaceutical industry and more recently some academic centers have streamlined a number of early processes to identify molecules which possess suitable characteristics to make acceptable drugs. This review will look at key preclinical stages of the drug discovery process, from initial target identification and validation, through assay development, high throughput screening, hit identification, lead optimization and finally the selection of a candidate molecule for clinical development.

A drug discovery program initiates because there is a disease or clinical condition without suitable medical products available and it is this unmet clinical need which is the underlying driving motivation for the project. The initial research, often occurring in academia, generates data to develop a hypothesis that the inhibition or activation of a protein or

pathway will result in a therapeutic effect in a disease state. The outcome of this activity is the selection of a target which may require further validation prior to progression into the lead discovery phase in order to justify a drug discovery effort (Figure 1). During lead discovery, an intensive search ensues to find a drug-like small molecule or biological therapeutic, typically termed a development candidate, that will progress into preclinical, and if successful, into clinical development (Figure 2) and ultimately be a marketed medicine.

Drugs fail in the clinic for two main reasons; the first is that they do not work and the second is that they are not safe.

Definitions given by client related to the molecules:-

1. Novel - New molecular targets
2. Me-too - Generics/biosimilars which have many drugs available (example in template: dopamine D2 partial agonist; dopamine agonist)
3. Augmented - Existing molecule products with new delivery format or device in addition to existing form; combinations of existing products;
4. Extensions - Existing molecule but new indication/label extension. [4]

Discovering New Therapeutic Uses for Existing Molecules:-

Discovering New Therapeutic Uses for Existing Molecules (New Therapeutic Uses) is a collaborative program designed to develop partnerships between pharmaceutical companies and the biomedical research community to advance therapeutics development. This innovative program matches researchers with a selection of pharmaceutical industry agents to test ideas for new therapeutic uses, with the ultimate goal of identifying promising new treatments for patients.

Therapeutic development is a costly, complex and time-consuming process. The average length of time from target discovery to approval of a new drug is about 14 years. The failure rate during this process exceeds 95 percent, and the cost per successful drug can be $2 billion

or more. The high therapeutic development failure rate means there are many existing, partially developed therapeutic candidates that could be repurposed for use in a new disease indication. Bringing together the best agents from pharmaceutical companies with the best new ideas from academic researchers could produce new treatments much more quickly than starting from scratch.

Launched in May 2012, NCATS' New Therapeutic Uses program helps re-engineer the research pipeline using an innovative strategy to identify new uses for agents that have undergone significant research and development by industry, including safety testing in humans. By using agents that already have cleared several key steps in the development process, scientists nationwide have a strong starting point to contribute their unique expertise and accelerate the pace of therapeutics development. [5]

Over the past decade, the number of new therapies developed for the treatment of rare diseases continues to increase. The most rapid growth has been in the development of new drugs for oncology indications. One focus in drug discovery for oncology indications is the development of targeted therapies for select patient subgroups characterized by genetic alterations. The identification of these patient subgroups has increased in the past decade and has resulted in a corresponding increase in the development of new drugs for genetically defined patient subgroups. [6]

The European Medicines Agency (EMA)

The European Medicines Agency (EMA) is responsible for assessing applications for drug licenses within the European Union (EU). New cancer drugs in the EU are licensed through the EMA, using a process called the centralized (or community) authorization procedure. This procedure is compulsory for new cancer drugs and gives a marketing authorization (licensee) for all EU member states, plus Iceland, Liechtenstein and Norway. Once a drug has EU marketing authorization, it is ‘licensed’, ‘registered’ or ‘approved’. All these terms mean the same thing. [7]

There were more than 17,000 projects (i.e., unique molecule-indication combinations) in clinical development and a total of about 12,000 products (or new medicines that would be submitted for FDA review as NMEs) in development.

- ***Preclinical research*** accounted for the highest number of projects (over 9,000) and potential new medicines (over 6,500). These figures are likely an underestimate, as much preclinical research activities may not yet have been the subject of news or analyst coverage or may only be known to the researchers and manufacturers involved, and therefore would not yet be reflected in the dataset.

- Over 5,400 new products were in***clinical development*** (defined in this report as products in Phase I, II, III, or having been filed with the FDA, or approved by the FDA, but not yet on the market in the U.S.). Since a single *product* may be investigated for multiple indications, and because the data include additional indications for products already approved and on-market, the number of pipeline *projects* in clinical development is larger, or about 8,000.
- Consistent with previous studies showing high attrition rates between Phase II and the much more expensive and lengthy Phase III clinical trial stage, there were many fewer compounds at each progressive phase of development. Whereas there were 2,329 molecules recorded in Phase II clinical
- Trials, there were only 833 products in Phase III trials. A total of 82 products in the dataset had completed Phase III clinical trials and had either been filed with the FDA or were approved by the FDA, but had not yet been launched in the U.S.[8]

STUDY OBJECTIVE

To identify the attributes of pipeline molecules for given indications in particular countries.

METHODOLOGY

Study area – Secondary Research conducted over pipeline molecules in countries all over the world.

Study tool and Data collection – Secondary Asset Focus Register containing data related to 4084 molecules which are under trials in different countries, for different indications are collected from IMS Internal Resources and company websites, etc. for validation purpose. **Figure 4** is the Asset Focus Register illustrating attributes taken into account while screening molecules

Inclusion criteria-Currently active trials in focused indications will be included on the Asset Database.

- **There are a few important characteristics that a molecule must have to be considered for drug development:**

  - It must be selective in the way it interacts with proteins to ensure that it only acts on the disease protein
  - It cannot be toxic
  - It must be distributed in the body in a way that ensures it reaches the disease site, it needs to be easily manufactured
  - It needs to be something that no-one has discovered – or more importantly, patented – before

Exclusion criteria – Removed molecules in phases; discovered, discontinued, suspended, withdrawn and marketed.

Figure4: Pictorial description of the Asset Focus Register

Product ID				Clinical Aspects										Commercial rights			Validation sources		
				Indication															
Sr No.	Asset Name	Company	Country (R&D focus geography)	Primary Indication (Indications in scope)	Sub Indication/s	Side effect linked to cancer (Yes/No)	Phase of Develoment for indication in scope	Product Marketed for other indications (Yes/No)	Trial site (Country/ies)	Mechanism of Action	Mode of Action (1. Novel; 2.Me-too; 3.Augmented-delivery mode/Combn ; 4.Extensions)	Device/Technology (Yes/No)	Mode of Adminstration	Licensee	Licensor	Licensing Availability (Yes/No)	Company website (CW)	Clinical trials website	Additional sources

- IMS Internal sources used as the main source of information
- Company websites were used for validating the Phase and Licensing details

Screening the database for potential assets - Asset Focus

Database of pipeline products created and screened in order to create a focus list of candidates.

1. **Asset Register Database created**-Input taken from IMS Internal sources related to 4084 molecules on the basis of indications in scope.
2. **Inactive molecules removed** – Deleted inactive molecules from Asset Register database.
3. **Molecules filtered by Trial phase** – Removed molecules in phases; discovered discontinued, suspended, withdrawn and marketed.
4. **Vaccines removed** – Filtered out the vaccines from the Asset Register.

Various search strings were used that were cancer related or not related to cancer for studying molecules in active development stage.(as seen in **Annexure 1**).

Screening process involved many inclusion and exclusion criteria and scoring criteria.

Molecules as demanded by the healthcare company were screened based on many scoring criteria that included urgency, development risk, cancer indication, indications, ownership, unmet needs as given in **Table 2**.

1. **Urgency –**According to the clinical trial stages, molecules were scored as most attractive or least attractive. Molecules in Phase 3 were given preference**.**
2. **Development risk –**According to the definitions taken molecules were classified (**Table 3**) into Novel, Me-too, Augmented and Extensions. Out of these Me-Too/Augmented were given higher rating.
3. **Cancer indication –** Molecules linked to cancer were preferred.
4. **Indications** – Indications were divided into high, moderate and less priority and scored accordingly as given in **Table 5.**
5. **Company type** – Scoring criteria was list of companies in a particular ranking order given by the client and they were classified as Small pharma, big pharma, Medium pharma and University. University was given importance as it's easier to buy molecules from a university or small pharma rather than big pharma companies**.** Molecules owned by universities will be considered more attractive.
6. **Ownership –**Molecules which are related to a licensee are given less priority.
7. **Unmet needs –**Indications were given score according to the company's requirement and then molecules were categorized high (3), medium (2), and low (1) and very low (0) as given in **Table 4**. Molecules with highest score were most attractive to the client.

Table 2: Scoring criteria for the molecules in active development stages

	Most attractive ⟷ Least attractive			
	Score			
Criteria	3	2	1	0
Urgency	Phase 3	Phase 2	Phase 1	Pre-clinical
Development risk/cost	Me-too / augmented	Extension	Novel	
Cancer indication	Linked to cancer			Not linked to cancer
Indication	High priority	Moderate Priority	Low priority	
Company type	University	Small Pharma	Medium Pharma	Big Pharma
Ownership	Licensor			Licensee
Unmet need	High	Medium	Low	Very low

Table3: Definitions that were taken into account while scoring the Development risk.

Novel	New molecular targets
Me-too	Generics/Bio-similar which have many drugs available (example in template: dopamine D2 partial agonist; dopamine agonist)
Augmented	Existing molecule products with new delivery format or device in addition to existing form; combinations of existing products;
Extensions	Existing molecule but new indication/label extension

Table4: Scoring criteria taken into account for unmet needs of the molecules.

Indication	Unmet need score
Nausea & vomiting	1
Hair loss	2
Hot flushes	0
Neutropenia	2
Anemia	0
Diarrhea	2
Mucositis	2
Sexual dysfunction	2
Neuropathy	3
Anorexia+ Cachexia	1
Thrombocytopenia	1
Rash	1
Fatigue	3
Depression	2
Stress + other psych issues	2
Infection	1

Table 5: Indications screened and scored based on the given priority table

Indications priority	
High Priority	Nausea and vomiting , hair loss , Mucositis
Moderate Priority	Fatigue , diarrhea , neuropathy
Low Priority	Infection, depression, sexual dysfunction, hot flushes.

Hence, after all the scoring criteria were considered, new columns were added in the Asset Focus Register and all the molecules were scored. New columns were added in the Asset Focus Register as shown below **(Figure 5).**

Figure 5: Illustration of the columns added in Asset Focus Register while scoring the molecules

Scoring criteria						
Urgency	Development Risk /cost	Cancer indication	Indication	Company type	Ownership	Unmet need

ETHICAL CONSIDERATION

- **Confidentiality**- Privacy of the healthcare company and the data obtained about the molecules is maintained.
- **Authenticity**-Data provided about the molecules in the Asset Focus Register is accurate. Data provided is valid and reliable.

RESULTS

- Screening of the molecules according to the scoring criteria brought down the count of molecules from 4084 to 305 molecules in Asset Focus Register as shown below in **Figure 6.**
- The Final Asset Focus Register contained columns like Product ID, Clinical aspects, Commercial rights, Validation sources and total scores for 305 molecules.
- These 305 molecules would be evaluated by the Healthcare Company according to their needs and would plan to go for any of these molecules in future.

Figure 6: Creating a shortlist of candidate assets

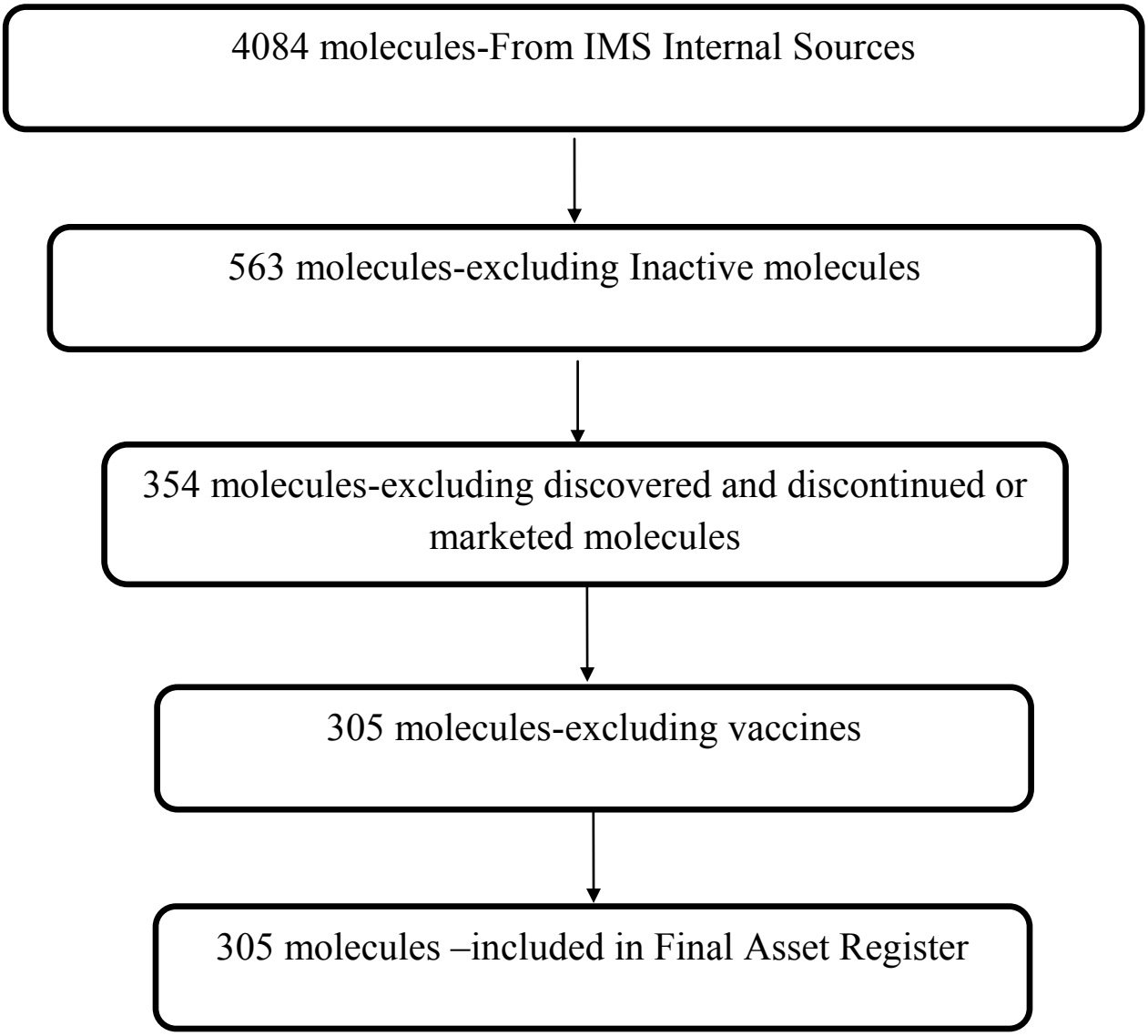
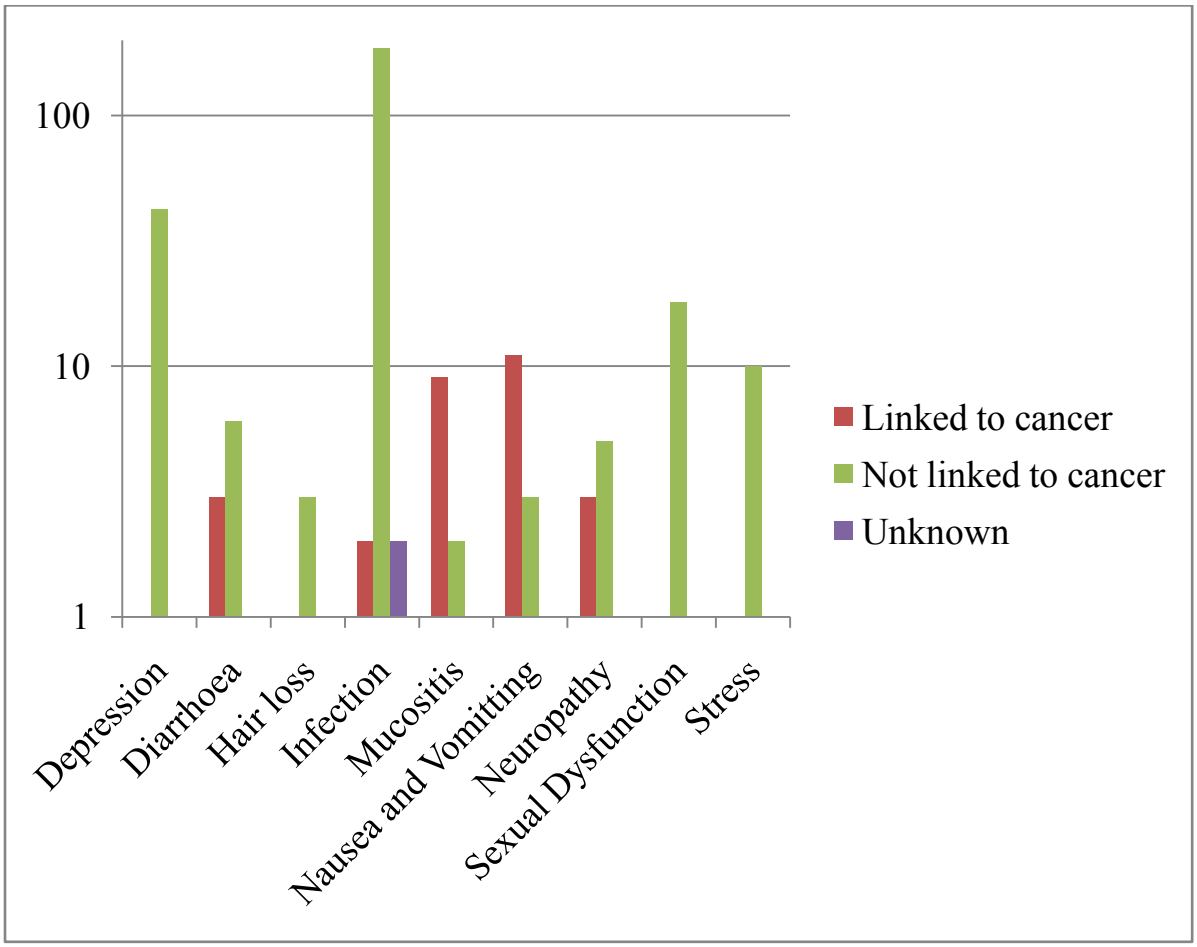


Table 6 : 305 Molecules sub-divided according to Indications

Indication	Molecules Analyzed	Linked to cancer	Not linked to cancer	Unknown
Depression	42	0	42	0
Diarrhoea	9	3	6	0
Hair loss	4	1	3	0
Infection	189	2	185	2
Mucositis	11	9	2	0
Nausea and Vomitting	14	11	3	0
Neuropathy	8	3	5	0
Sexual Dysfunction	18	0	18	0
Stress	10	0	10	0
Total	305	29	274	2

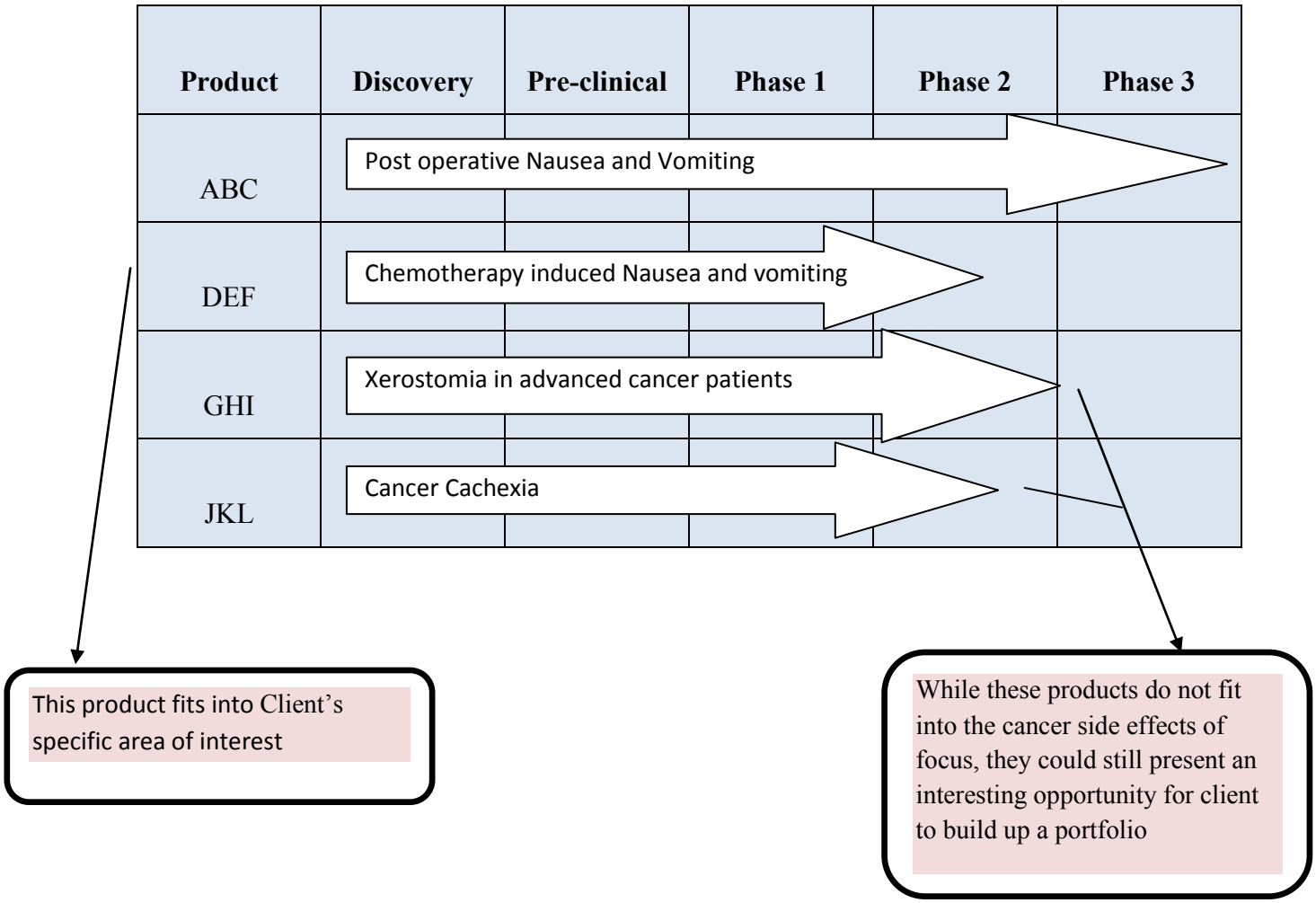
Figure 7: Graph showing molecules that are linked to cancer or not linked to cancer



CONCLUSION

- The database containing all products in active development for specific indications (cancer side effects) were of interest to the client. Client's main focus was molecules in active development related to 11 indications given all over the world. **Figure 7** explains client's area of interest.
- Search strings were created to extract assets by indications. For maintaining Database molecules were taken from the IMS Internal sources as it gives the most validated and reliable data and other references taken were company websites.
- Client then focused on particular criteria for scoring the screened out assets.
- Healthcare company found molecules most attractive that were:
  - ✓ Phase 3 in clinical trials,
  - ✓ Me-too/Augmented types,
  - ✓ Related to cancer,
  - ✓ Licensor should be a University or small pharmaceutical company,
  - ✓ Molecules with indications having high unmet needs

Figure 7: Client's area of interest while considering a molecule available in market



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ANNEXURE

Annexure 1: Search Strings Used

Indications	Related search strings(cancer related/associated/ induced
Stress	Cancer related stress
Fatigue	Cancer related fatigue
Depression	Cancer related depression
Hot flushes	Cancer related hot flushes
Sexual dysfunction	Infertility
	vaginal atrophy
	Dyspareunia
	retrograde ejaculation
	loss of sexual desire
	erectile dysfunction
	Anejaculation
	inability/decreased ability to reach orgasm
Nausea and vomiting	Emesis
	Alopecia
Infection	bacterial infection
	viral infection
	Pneumonia
	Flu
	Tonsillitis
	Listeria
	Bronchitis
	parasitic infection
	Pertussis
	CMV, thrush

Indications	Related search strings(cancer related/associated/ induced
	rhinovirus infection
	Cellulitis
	Bronchiectasis
	Herpes simplex
	Toxoplasmosis
	Septicaemia
Diarrhea	Diarrhea
Neuropathy	Cancer related neuropathy
Mucositis	Stomatitis