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Insights from Changing Landscape in New Product Development and Approvals in Pharmaceutical Industry: Recent Trends for Betterment of Humanity

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ABSTRACT: A drug approved today is the result of an idea generated 10-15 years back, which has now succeeded. It takes several years and huge resources to gain approval from the regulatory agencies, and bring a new medicine to the marketplace for the patients, by pharmaceutical companies engaged in new drug discovery and development. The purpose of this paper is to understand the strategic planning, therapeutic area focus and product selection being followed by the pharmaceutical companies while developing innovative products. This research sampled 210 new drug approvals granted by the USFDA over the 5 year period from 2014-2018, to study the type of drug (small molecules versus biologics versus peptides) getting approvals, contribution of in-house discovered products versus in-licensed products, approvals received by big pharmaceutical companies versus smaller biotech companies, and drug approvals by various therapeutic areas. This study found that in-licensed drug candidates (molecules) formed an important component of new drug approvals as a total of 65 new drug approvals originated from licensing activities. Further, it was observed that even though large pharma companies accounted for a total of 153 new drug approvals, smaller biotech companies also rallied in with 57 new drug approvals pointing out to a changing landscape in drug development. This study analyzed the new drug approvals pursued by pharmaceutical and biotech companies in different therapeutic areas for the betterment of humanity, and found that oncology (cancer) therapeutic area had 63 new drug approvals, followed closely by 36 new approvals in the infectious disease space. The contributions made through this study on new product development and approvals would be useful for management of research and development of innovative products, licensing strategy and portfolio planning in the pharmaceutical industry.

Keywords: Product development, Drug development, USFDA, new drug approvals.

Abbreviations: USFDA, United States Food and Drug Administration; AIDS, Acquired immunodeficiency syndrome; CDER, Centre for Drug Evaluation and Research; CBER, Centre for Biological Evaluation and Research; IND, Investigational New Drug; NDA, New Drug Application; ADC, Antibody-drug conjugates.

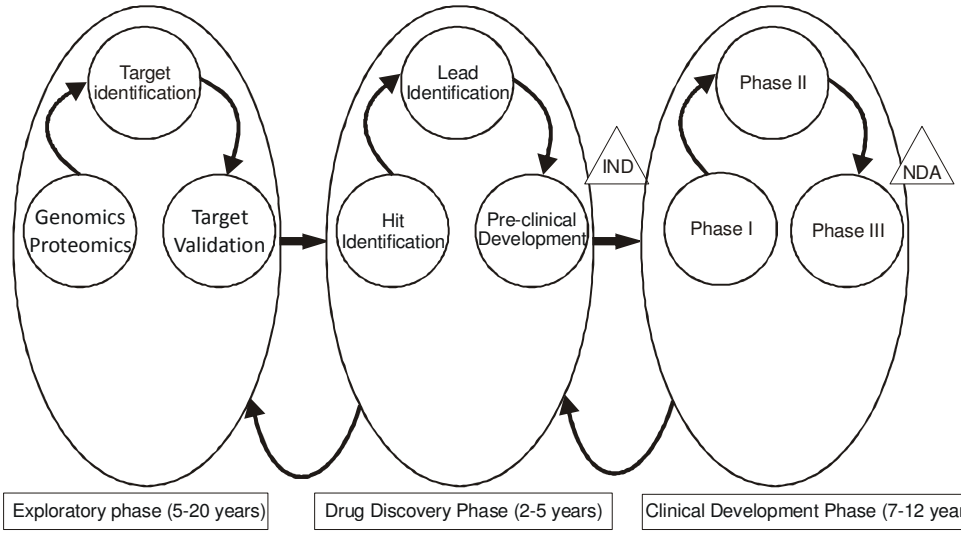
I. INTRODUCTION

The pharmaceutical and biotechnology industry has been developing new drugs over the last several decades [1]. Several new drugs have been developed to treat hitherto deadly and untreatable diseases like cancer, heart disease, diabetes, asthma, kidney diseases, liver diseases, infectious diseases like flu or Acquired Immune Deficiency Syndrome (AIDS), and this has led to betterment of human health. New drug discovery and development takes on an average eight to ten years to bring a drug from concept to approval by the regulatory agencies, and there is a huge chance of failure [2]. The regulatory agencies have become more and more stringent over the last many decades, and as a result of this the drug development process has become more regulated and expensive [3].

United States of America (USA) leads the world in the largest number of new drug approvals. The pharmaceutical industry has witnessed several licensing deals where big pharmaceutical companies have licensed candidates (molecules) under development from other companies, biotech's and research institutes [4-6]. The United States Food and Drug Administration (USFDA) is the regulatory agency that regulates the approval of new drugs in the United States. Centre for Drug Evaluation and Research (CDER) reviews small molecules and Centre for Biological Evaluation and Research (CBER) reviews biologic applications.

Several medicines have been discovered using small molecules, peptides, biologics, RNAi and other approaches. However, it takes several years before a new drug is granted approval for use in humans [7]. The process for development of a new drug can be broadly classified into three phases, 1. Exploratory phase, 2. Drug discovery phase and 3. Clinical development phase. The exploratory phase starts with target identification i.e. identifying the molecular target in the body, either a nuclear receptor, enzyme, protein, nucleic acid etc., and followed by validation of the target. The drug discovery phase starts with the identifying hits using either small molecule approach, biologics approach, gene therapy approach, or a combination of these along with suitable drug delivery approaches to develop molecules (candidates) for a particular target in the human body. Then a set of *in-silico*, *in-vitro* and *in-vivo* assays are developed that can be used to decide the affinity of the candidate to the target and study the efficacy and safety of the candidate. The selected candidate is then evaluated through a set of studies required for Investigational New Drug (IND) enabling efficacy, safety and toxicology studies. The IND application is then filed with the USFDA for permission

to conduct Phase I clinical trials in humans. For most of the indications, the Phase I trials have to be conducted in healthy human volunteers, however, for certain indications like cancer (oncology), the regulatory agency grants permission to conduct Phase I trials in patients. The Phase I trials provide vital information like the safety and pharmacokinetic profile of the drug in humans at several doses. Once the safety profile of the candidate is established, the permission is then granted to conduct Phase II studies in small number of patients to establish the safety and efficacy of the candidate. The Phase III trials are conducted in a larger patient population and may vary in number of patients to be evaluated, duration of clinical trial etc., depending in the indication [8]. Once the Phase III trial results are available, the New Drug Application (NDA) is then compiled and filed with the USFDA [9].



Source: Author compilation. (IND = Investigational New Drug, NDA = New Drug Application)

Fig. 1. Drug Discovery and Development Process.

The USFDA takes ~12-18 months to review the NDA application and either approve or reject the NDA. There are disease area specific groups within the USFDA which reviews the various drug applications [10]. Opinion is also sought from an external advisory group before the final recommendation by the USFDA. Once the approval is granted to a new drug, the details of its generic name, brand name, patent status and exclusivity status are also recorded in the USFDA orange book.

There were 46 new drug approvals granted by USFDA in the year 2017 [10, 11], and 59 new drug approvals granted by USFDA in the year 2018 [12, 13]. The 59 new drug approvals granted in the year 2018 were further analyzed by the type of the drug, and it was reported that 17 new biological received approval in the year 2018 [14]. The previous study reported the analysis over a one year period. The role of licensed molecules versus in-house discovered molecules as well as the approvals received by big pharmaceutical companies versus smaller biotech companies were not analyzed in previous studies. This current study aimed to analyze the new drug approvals over a longer period of five years from 2014-2018. This proposed approach in this research will be useful to study the type of drug (small molecules versus biologics versus peptides) getting approvals, contribution of in-house discovered products versus in-licensed products, approvals received by big pharmaceutical companies versus smaller biotech companies, and drug approvals by various therapeutic areas over the longer period of 5 years from 2014-2018.

II. OBJECTIVES AND METHODOLOGY

Following were the objectives of the study:

– To evaluate the number of new drug approvals in the United States of America during the last 5 years (2014-2018).

– To evaluate the number of biologics approvals versus small molecule approvals for understanding the current focus of pharmaceutical companies in drug development. Biologics are large and complex molecules and enjoy a greater exclusivity period of 12 years with the USFDA thereby prompting many pharmaceutical and biotech companies to develop Biological.

– To study the drug approvals received from big pharma as well as smaller companies and biotech companies to confirm the widely believed concept that large pharmaceutical companies have greater access to resources and capabilities required for drug development, registration and commercialization [16]. Hence, big pharma should have more number of drug approvals from the USFDA.

– To study the percentage of new drug approvals that resulted from in-licensed assets. Biotech companies and research institutes often license their assets to big pharma for further development and commercialisation.

– To study the new drug approvals of companies in different therapeutic areas over the last five years and examine which therapeutic areas have the greatest focus in new drug development.

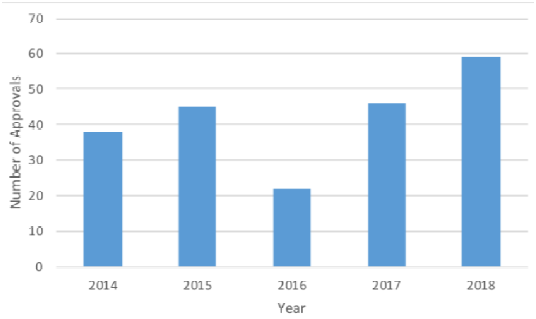
The new drug approvals granted by USFDA over the years 2014-2018 were collected based on secondary data analysis. The number of drugs approved were further analyzed based on their structure and classified into small molecule drugs and biologics. The originators and licensees of the drugs were analyzed and grouped into large pharma and biotech's to understand the newer trends in drug development by companies.

The new drugs were then classified by therapeutic areas to understand the strategy of pharmaceutical companies and their therapeutic areas of interest.

III. RESULTS AND DISCUSSION

A. New Drug Approvals

The number of new drug approvals from the year 2014-2018 are shown in Fig. 2. In the year 2014 there were 38 new drug approvals, 45 in the year 2015, 22 in the year 2016, 46 in the year 2017 and 59 new drug approvals in the year 2018. The year 2016 had the lowest number of new drug approvals while the year 2018 had the largest number of new drug approvals by the USFDA. Further, the breakup of the new drug approvals with respect to small molecules, biologics, peptides are given in Table 1.



Source: Author compilation from www.fda.gov

Fig. 2. New Drug Approvals in the Year 2014-2018.

B. Small Molecules, Peptides and Biologics Approval

Small molecules are chemically synthesized and can be taken orally. Peptides are molecules containing two or more amino acids and are linked by peptide bonds. Peptides can be manufactured either by solid phase or solution phase synthesis. Biologics are large molecules, produced either in yeast, bacterial or mammalian cell-lines, and come in the form of therapeutic proteins, monoclonal antibodies, bi-specific antibodies, antibody-drug conjugates (ADC) etc. Biologics are delivered via injections or infusions to the human body. Biologics enjoy longer exclusivity periods with the USFDA. Biologics are also difficult to copy and establish structural comparability unlike small molecules where generics can be easily made. Majority of the best selling drugs are based on biologics approach. Further, biologics offer a more targeted approach in many cases and hence should be the preferred approach for developing drugs for several diseases such as cancer, rheumatoid arthritis, spondylitis, Crohn's disease, etc.

It may be seen from Table-1 that the total number of new drug approvals during the last five years (2014-2018) have increased from 38 to 59. However, the analysis of the number of new biologics approved as compared to small molecules showed that there were 5 biologics approved in the year 2014, 11 in the year 2015, 7 in the year 2016, 12 in the year 2017 and 17 in the year 2018.

On the other hand, there were 27 small molecules approved in the year 2014, 30 in year 2015, 10 in year 2016, 28 in year 2017 and 40 in year 2018. In addition, there were 4 peptide based therapies approved in the year 2014, 1 in the year 2016 and 3 in the year 2017.

Table 1: Small molecules, biologics, peptides approved in the year 2014-2018.

Year	Number of approvals	Small Molecules	Biological	Peptides	Others
2014	38	27	5	4	2
2015	45	30	11		4
2016	22	10	7	1	4
2017	46	28	12	3	3
2018	59	40	17		2

C. Large Pharmaceutical Companies versus Biotech's

Large pharmaceutical companies focus on innovation and have huge resources in terms of budgets, skills, capabilities and experience in clinical development, manufacturing, regulatory processes and commercialisation capabilities. On the other hand, smaller biotech firms would ideally like to license the candidates to large pharmaceutical companies at different stages for further development.

This study analysed the number of new drug approvals secured by large pharmaceutical companies and biotech companies. There were 4 approvals by biotech's in 2014, 9 in 2015, 7 in 2016, 12 in 2017 and 25 in 2018. It is important to note here that there were 22 overall approvals in the year 2016, and of that 31 % of the new drug approvals were received by biotech companies. This trend continued in the year 2017 and 2018. This signifies that capital was available to the biotech companies from the market or through innovative funding models to conduct expensive developmental studies required for approvals.

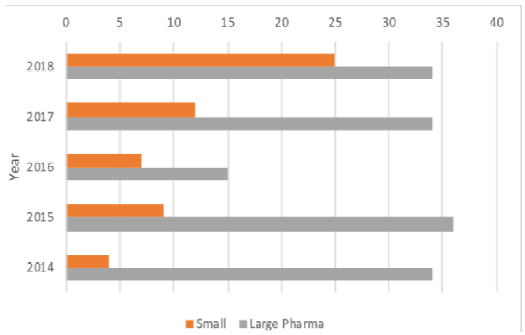


Fig. 3. Approvals received by Large Pharma's versus Biotech's [2014-2018].

D. In-house discovered molecules versus licensed candidates (molecules)

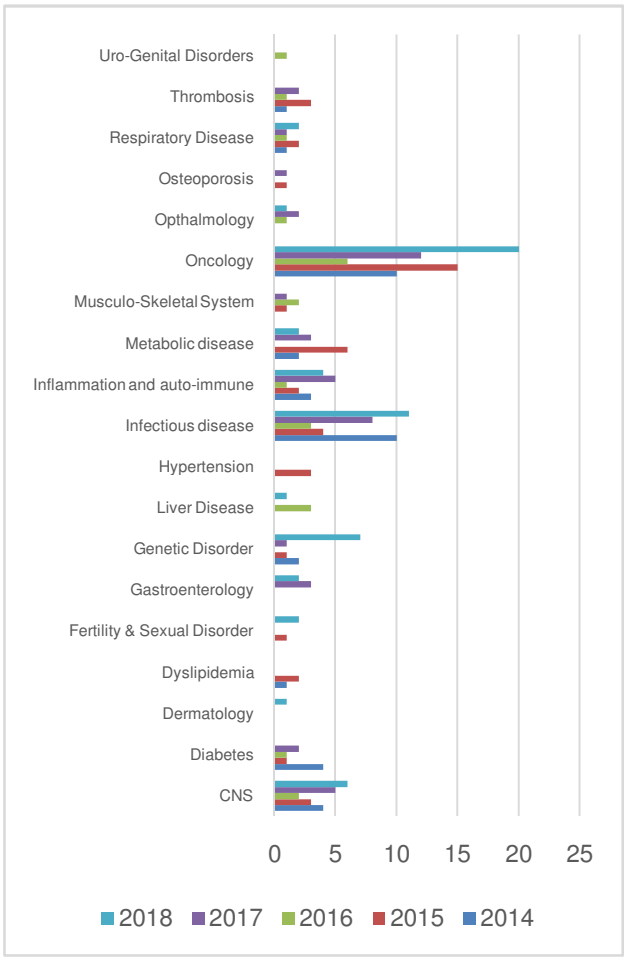
Big pharma companies gain access to breakthrough assets in discovery or development stage from biotech companies or research institutes. On the other hand from a biotech's perspective, the big pharma would represent more resources and expertise in drug development [17-20]. This study analysed the number of new drug approvals and how many programs were licensed by big pharma from biotech companies. It is found that 8 of the 38 new drug approvals in 2014 were in-licensed from biotech's representing a 21 % share of the total new drug approvals. In 2015, 18 programs out of 45 new drug approvals were in-licensed representing a 47% share. In 2016, 6 of 22 programs were in-licensed. In the year 2017, 20 of 46 new drug approvals were in-licensed programs, representing a 53% share, while in the year 2018, 13 of 59 programs were in-licensed programs.

Table 2: Number of in-licensed programs that received NDA approval [2014-2018].

Year	In-licensed programs	Number of approvals	Percentage of in-licensed programs
2014	8	38	21
2015	18	45	47
2016	6	22	16
2017	20	46	53
2018	13	59	34

E. Drug approvals by therapeutic area

Pharmaceutical companies develop drugs in different therapeutic area. This research classified drugs by therapeutic area to identify which area had more focus by companies and regulators in receiving more new drug approvals. The results of this analysis across therapeutic areas namely Central Nervous System (CNS), Diabetes, Dermatology, Dyslipidaemia, Fertility & Sexual Disorder, Gastroenterology, Genetic Disorder, Liver Disease, Hypertension, Infectious disease, Inflammation and auto-immune, Metabolic disease, Musculo-Skeletal System, Oncology, Ophthalmology, Osteoporosis, Pain , Respiratory Disease, Thrombosis and Uro-Genital Disorders are provided in the below Fig. 4.



Source: Author compilation from www.fda.gov

Fig. 4. New drug approvals by therapeutic area [2014-2018].

IV. DISCUSSION

The results of this study shows that the number of new drug approvals were consistent across the years 2014-2018, except for the year 2016 which reported only 22 new drug approvals. Companies are increasingly using recent advances in machine learning and artificial intelligence in drug discovery and development [21]. This research found that companies are increasing focus on developing biologic based therapies. This is encouraged by ease of administering biologicals due to availability of newer technologies as also by the fact that novel biologics provide a greater exclusivity period and are difficult to make generic copies [22].

Traditionally, big pharma companies were expected to gather new drug approvals. This study points out to the fact that biotech's are increasingly gaining new drug approvals. This is possible due to the funding ecosystem prevalent in the United States and the fact that biotech's are getting funded by IPO's and other similar mechanisms. Clinical Research Organisations (CRO's) also provide their expertise in drug development and regulatory affairs, which biotech companies can utilise to complete clinical trials and secure new drug approvals.

This study revealed that on an average 34 % of new drug approvals originated from licensing deals. Thus, licensing played a very important role in the search for new drugs. Companies should increasingly collaborate and use complementary capabilities to pursue new drug development.

There are different regulatory requirements in different therapeutic areas like Central Nervous System (CNS), Diabetes, Dermatology, Dyslipidemia, Fertility & Sexual Disorder, Gastroenterology, Genetic Disorder, Liver Disease, Hypertension, Infectious disease, Inflammation and auto-immune, Metabolic disease, Musculo-Skeletal System, Oncology, Opthalmology, Osteoporosis, Other, Pain , Respiratory Disease, Thrombosis and Uro-Genital Disorders. Also different therapeutic areas have different unmet medical needs and a different market potential for pharmaceutical companies investing in expensive drug development in these areas. The results of analysis found that Oncology had the maximum number of new drug approvals over the years 2014-2018, followed closely by infectious diseases and CNS disease.

V. CONCLUSION

This study offers useful insights to researchers, scientists, pharmaceutical company managers and leaders in biotech companies and pharmaceutical companies on different aspects of drug development and recent trends of new drug approvals by the USFDA. These insights would be useful for management of Research and Development of innovative concepts, strategy, as well as portfolio planning in the pharmaceutical industry. With the advancement in science, pharmaceutical companies are making immense contribution to betterment of human health and solving many of the hitherto deadly diseases affecting mankind by developing drugs that target unmet medical needs. Newer technologies have made it possible to discover and develop complex drugs in a consistent manner. Regulatory agencies like the USFDA have consistently guided the pharmaceutical companies

in drug development and ensured the safety of the patient population. The pharmaceutical industry has been actively contributing to the economy and unmet needs in healthcare by maintaining very high levels of innovation.

VI. FUTURE SCOPE

The study has the following limitations. This study covers only new drug approvals trends in the United States of America. Future studies should study the new drug approvals in Europe and Japan and compare the trends in USA, Europe and Japan.

Conflict of Interest. The authors declare no conflict of interest. The views presented in this paper are those of the authors only and do not represent the views or opinions of the institutes to which they are affiliated.

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