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TO STUDY AND ASSESS ORPHAN DRUGS APPROVED BY US FDA FROM 2009 TO 2018.

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ABSTRACT **BACKGROUND:** Orphan drugs are "drugs or biological products for diagnosis/treatment/ prevention of a rare disease or condition for which no reasonable expectation that cost of developing & marketing will be recovered from sales of that drug". WHO defines orphan/rare diseases as, 'all pathological conditions that affect 0.65-1 of every 1000 inhabitants'. While ICMR defined orphan diseases when it affect '<1 in 2500 individuals. The Orphan Drug Act (ODA) was passed on January 28, 1983 to stimulate the research, development and approval of products that treat orphan diseases. **OBJECTIVE:** To study and assess orphan drugs approved by US FDA from 2009 to 2018. **METHODOLOGY:** Data of orphan drugs approved from 2009 to 2018 was obtained from US FDA website. Data was assessed as- Number of drugs approved yearly, Approval for rare/non-rare diseases, Nature of drugs approved (biological/non-biological), Approved as novel drug product, new/expanded indication, not a novel product but use in rare disease or other non-novel orphan approval, Therapeutic class of orphan drug approved, Pharmaceutical companies marketing the drugs. **RESULTS:** From 2009 to 2018, total 426 orphan drugs were approved by US FDA. 155(36.38%) were biologicals and 271(63.61%) were non- biologicals. Out of 155 biologicals, 97 (62.58%) were monoclonal antibodies. 384(90.14%) were approved for rare diseases and remaining 42 for non- rare diseases. Out of total drugs approved 264(61.97%) were novel drug product, 133(31.22%) approved for new/expanded indication, 13(3%) were not novel product but use in rare disease and 16(3.75%) were non novel orphan approvals. Out of 426 drugs 195 (45.77%) were approved for cancer treatment remaining 52 for immunological disorders, 39 for metabolic and endocrine disorders, 35 for genetic disorders, 21 were antimicrobials, 30 for haematological disorders, 6 for diagnostic purpose, 4 were vaccines. Out of 426 orphan drugs 389(91.31%) were innovated by USA pharmaceutical companies and remaining by companies from United Kingdom, France, Switzerland, Germany, Canada. Indian companies innovated 1 orphan drugs for 2 new indication. **CONCLUSION:** 426 orphan drugs approved by US FDA from 2009 to 2018. Most of them were for cancer treatment and majority of them were monoclonal antibodies. Maximum numbers of drugs were innovated by USA pharmaceutical companies.

KEYWORDS : Rare Diseases, Novel Drug, Orphan Drug Act.

INTRODUCTION

Drugs or biological products for diagnosis/treatment/ prevention of a rare disease or condition for which no reasonable expectation that cost of developing & marketing will be recovered from sales of that drug.[1] WHO defines orphan/rare diseases as, 'all pathological conditions that affect 0.65-1 of every 1000 inhabitants' While ICMR defined orphan diseases when it affect '<1 in 2500 individuals'. These diseases are like children without parents.[2,3]

There are ~ 6,000 orphan diseases, out of which 80% are genetic. A disease can be rare in a region but may be very common in another region (IgA nephropathy is common in Asia and Africa, but rare in European Union).[4]

Orphan drugs are intended for diseases with a very low prevalence, and many countries have implemented legislation to support market access of orphan drugs.[5]

Medical melodrama in early 1980's in US, set the pace for concept of orphan drug and its regulation. A young boy with Tourette syndrome, generated public opinion for unfortunate victims of these diseases. National organisation for rare disorders (NORD) formed by supporters and families of patient with rare diseases. Then Orphan Drug Bill was passed in 1981 in US. Absence of specific treatment for orphan disease causes psychological distress to patient and family, and a feeling of hopelessness sets in. USA was first nation to propose a legal framework to encourage development and availability of orphan drugs. The Orphan Drug Act (ODA) was passed on January 28, 1983 to stimulate the research, development and approval of products that treat orphan diseases.[6]

Lots of issues complicate the drug development process of rare diseases, for example, less understood pathophysiology, lack of validated preclinical models, less research, and lack of standard comparator drug. Clinical issues such as lack of information about natural history of the disease, poorly defined endpoints, poor trial design and inadequate sample size, recruitment problems, lack of well-defined diagnostic criteria, and other issues such as non-existent comparator drug and funding problems. Although multicentric trials can short out this issue, it has own drawback such as lack of consistency in diagnostic facility in small centres and regional sociocultural variation.[7]

Like other drug development, orphan drug developmental is also a costly process. Industries show negligible interest in the development of treatment for rare diseases as there is less return on investment. Mostly, orphan drug research is dependent on government incentives. USFDA, EMEA, Japan, and many other countries offer benefits such as protocol assistance, fast-tract approval, waiver of fees, and marketing exclusivity.[8]

Coming to the Indian scenario, so far, ~450 rare diseases have been identified in India. It was statistically estimated that, in India, the rare disease and disorder population was 72,611,605 as per published data of national population census of 2011. Now, the awareness for rare disease is increasing. India has reportedly higher rare diseases population than the world average, but initiatives from government side are still less, and in fact, India lacks national legislation for orphan medicines and rare diseases, in spite that these are most populated countries.[9]

MATERIALS AND METHODS

Data of orphan drugs approved from 2009 to 2018 was obtained from US FDA website. Data was assessed as-

1. Number of drugs approved yearly
2. Approval for rare/non-rare diseases
3. Nature of drugs approved (biological/non-biological)
4. Approved as novel drug product, new/expanded indication, not a novel product but use in rare disease or other non-novel orphan approval
5. Therapeutic class of orphan drug approved
6. Pharmaceutical companies marketing the drugs

Descriptive statistics were used to analyses the data. The data were

expressed as percentage.

RESULTS

From 2009 to 2018, total 426 orphan drugs were approved by US FDA.

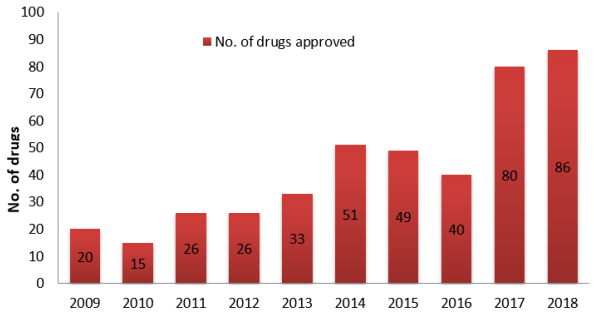

Figure 1 - Number of drugs approved yearly

US FDA approved 20 orphan drugs in 2009, 15 in 2010, 26 in 2011, 26 in 2012, 33 in 2013, 51 in 2014, 49 in 2015, 40 in 2016, 80 in 2017, and 86 in 2018. (figure 1)

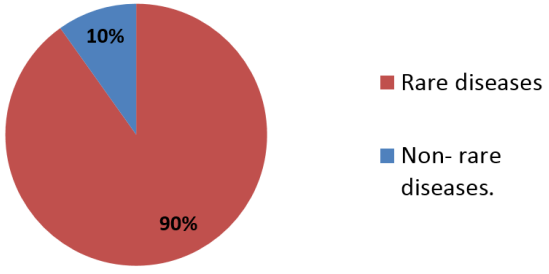

Figure 2- Approval for rare/non-rare diseases

384(90.14%) were for rare diseases and remaining 42 for non-rare diseases. (figure 2)

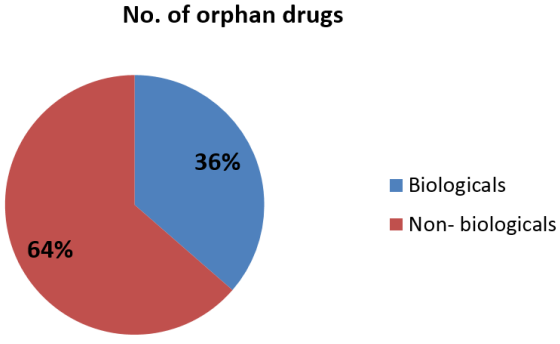

Figure 3 - Nature of drugs approved (biological/non-biological)-

155(36.38%) were biologicals and 271(63.61%) were non-biologicals. Out of 155 biologicals, 97 (62.58%) were monoclonal antibodies. (figure 3)

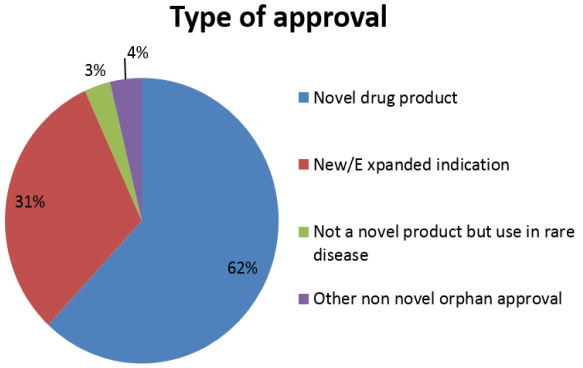

Figure 4 -Approved as novel drug product, new/expanded indication, not a novel product but use in rare disease or other non-novel orphan approval

Out of total drugs approved 264(61.97%) were novel drug product, 133(31.22%) approved for new/expanded indication , 13(3%) were not novel product but use in rare disease and 16(3.75%) were non novel orphan approvals.

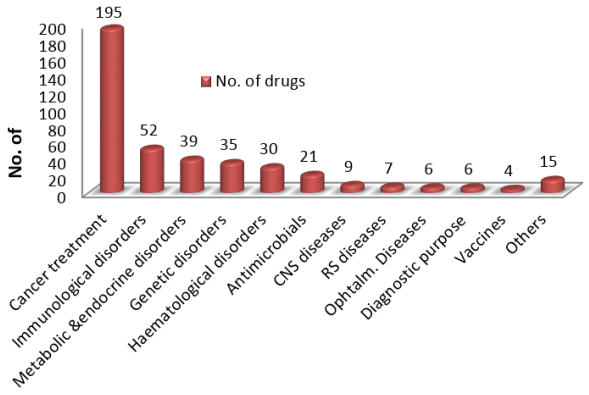

Figure 5- Therapeutic class of orphan drug approved

Out of 426 drugs 195 (45.77%) were approved for cancer treatment , 52 for immunological disorders, 39 for metabolic and endocrine disorders, 35 for genetic disorders, 21 were antimicrobials, 30 for haematological disorders, 6 for diagnostic purpose, 4 were vaccines.

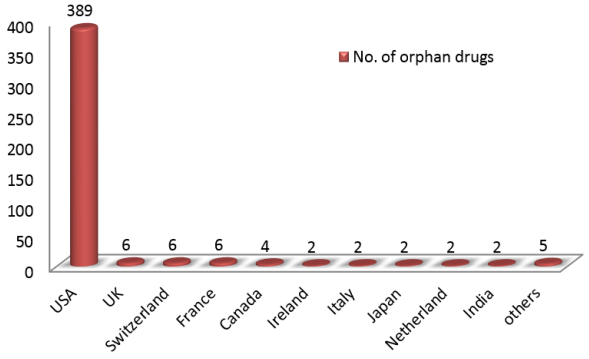

Figure 6- Pharmaceutical companies marketing the drugs

Out of 426 orphan drugs 389(91.31%) were innovated by USA pharmaceutical companies and remaining by companies from United Kingdom, France, Switzerland, Germany, Canada. Indian companies innovated 2 orphan drugs.

DISCUSSION

We analysed data about orphan drug approved from 2009 to 2018 available on US FDA website. In our study we found that there is increasing trend of orphan drugs approval from 2009 to 2018 (figure1). This shows that since passage of orphan drug act (ODA) in 1983, the structure of development incentives laid out in the legislation has successfully spurred investment and innovation in rare disease therapies.

Majority of orphan drugs were approved for rare diseases (90%). Only 10% of orphan drugs were approved for non rare diseases (figure2). Examples of orphan drugs approval for non rare diseases are bosentan (novel product) for treatment of pulmonary arterial hypertension (2017), tafenoquine (novel product) for treatment of malaria (2018), tacromilus (new indication) for prophylaxis of organ rejection in patients receiving allogeneic kidney transplant. (2018).

About 155 (36.38%) of orphan drugs approved were biologicals. Biologics are substance that is made from a living organism or its products and are used in the prevention, diagnosis, or treatment of cancer and other diseases. Biological drugs include antibodies, interleukins, and vaccines.[10] Out of 155 biologicals, 97 (62.58%) were monoclonal antibodies majority of which approved for treatment of cancer. 271(63.61%) of orphan drugs approved were non- biologicals (figure 3).

Out of total orphan drugs approved, 264(61.97%) were novel drug product. Novel drug product is an active compound, complex, molecule that previously has not been approved by the FDA. Novel

drugs are often innovative products that serve previously unmet medical needs or otherwise significantly help to advance patient care and public health. [11] Examples of novel drug products are mepolizumab for treatment of Churg-Strauss Syndrome (2017), ivacaftor for treatment of cystic fibrosis (2018), inotersen for treatment of transthyretin amyloidosis (2018). 133(31.22%) orphan drugs were approved for new/expanded indication of old drugs. Examples are eculizumab for treatment of Myasthenia Gravis (2017), adalimumab for treatment of non-infectious intermediate, posterior, or panuveitis (2018), pembrolizumab for treatment of Merkel cell carcinoma (2018), bevacizumab for treatment of fallopian tube carcinoma (2018). 13(3%) were not novel product but use in rare disease. Examples are botulinum toxin type A for dynamic muscle contractures in pediatric cerebral palsy patients (2016), romiplostim for treatment of immune thrombocytopenic purpura (2018), ivacaftor for cystic fibrosis (2018). 16(3.75%) were other non-novel orphan approvals. Examples are uridine triacetate as an antidote of 5-fluorouracil or capecitabine poisoning (2015), mebendazole for gastrointestinal infestations by Trichuris trichiura (whipworm), Ascaris lumbricoides (roundworm), Ancylostoma duodenale and Nectar americanus (hookworm) (2016) (figure 4).

Out of 426 orphan drugs 195 (45.77%) were approved for cancer treatment. This is because the expenditure on cancer drugs dominate pharmaceutical expenditure in developed markets, with worldwide sales at $107 billion in 2015, an increase of 11.4% since 2014.[12] Remaining 52 were for immunological disorders, 39 for metabolic and endocrine disorders, 35 for genetic disorders, 21 were antimicrobials, 30 for haematological disorders, 6 for diagnostic purpose, 4 were vaccines. (figure 5)

Out of 426 orphan drugs 389(91.31%) were innovated by USA pharmaceutical companies and remaining by companies from United Kingdom, France, Switzerland, Germany, Canada. Indian companies innovated 1 orphan drugs for 2 indication (gemcitabine ready-to-use premixed formulation of the IV cytotoxic chemotherapy for Treatment of ovarian cancer and pancreatic cancer). (figure 6) India has reportedly higher rare diseases population than the world average, but initiatives from government side are still less, and in fact, India lacks national legislation for orphan medicines and rare diseases.[13]

Limitations of our study was that we did not perform cost analysis of orphan drug approved from 2009 to 2018.

CONCLUSION

426 orphan drugs approved by US FDA from 2009 to 2018. Most of them were for cancer treatment and majority of them were monoclonal antibodies. Maximum number of drugs were innovated by USA pharmaceutical companies. As India is still in developing phase, there is setback in regulation and development in orphan diseases research. Therefore, there is a strong need in assessment of the spectrum and burden of orphan diseases and awareness program in mass regarding orphan disease. Strong policies and initiatives should be made by government and private institution for orphan drug development.

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