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Grants To Stimulate Product Development for Rare Diseases

M. P. Venkatesh[1]*, Sridhar S[2], Kavya Sravanthi G[3], T M Pramod Kumar[4]

[1]Pharmaceutical Regulatory Affairs Group, Department of Pharmaceutics, JSS College of Pharmacy, Jagadguru Sri Shivarathreeshwara University, S.S Nagar, Mysuru – 570015, Karnataka, India
[2]M.Pharm, Pharmaceutical Regulatory Affairs, Department of Pharmaceutics, JSS College of Pharmacy, Jagadguru Sri Shivarathreeshwara University, S.S Nagar, Mysuru – 570015, Karnataka, India
[3]M.Pharm, Pharmaceutical Regulatory Affairs, Department of Pharmaceutics, JSS College of Pharmacy, Jagadguru Sri Shivarathreeshwara University, S.S Nagar, Mysuru – 570015, Karnataka, India
[4]Department of Pharmaceutics, JSS College of Pharmacy, Jagadguru Sri Shivarathreeshwara University, S.S Nagar, Mysuru – 570015, Karnataka, India

Abstract : FDA is committed in advancing rare disease therapies through the development of orphan products. There are about 7000 rare diseases that collectively affect over 30 million people worldwide. The Orphan Drug Act (ODA) of 1983 was signed into law, which is one of the most important parts of health care legislation today. In the past decade before ODA was passed, only 10 treatments were available for rare diseases. The main objective of this study is to compare the situation of rare diseases before and after the developments of the products, and to know the clinical phases (I-IV) involved during the product development process slated for rare diseases. FDA receives funding's from the National Institute of Health (NIH) for the development of products for rare diseases. The growth of pharma industries has slowed in recent years for reasons such as patent expirations, generic competition and stringent regulatory guidelines. Orphan drugs may help pharma companies to reduce the impact of revenue loss caused by patent expires of blockbuster drugs. Although pharmaceutical industry faces many challenges, orphan drugs seem to offer the key for recovery and stability within the market. Rare diseases need more attention due to lack of proper diagnosis and treatment. To treat these rare diseases, USFDA has awarded 18 new research grants totalling more than $19 million to boost development of products for treating rare diseases. The implications of such findings for future development and marketing of therapies for rare diseases are developed.

Key Words : Orphan drug, Grants, Treatment, Funding.

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Introduction[1]

Rare diseases collectively account for significant unmet health care needs in the United States. A rare (orphan) disease is defined under the United States Orphan Drug Act amendment (Orphan Drug Act (1983); Health Promotion and Disease Prevention Amendments (1984) as a disorder that generally affects less than 200,000 individuals (0.07% of the US population). Rare disease research has reached a tipping point, with the confluence of scientific and technologic developments that if appropriately harnessed, could lead to key breakthroughs and treatments for this set of devastating disorders. Industry-wide trends have revealed that the traditional drug discovery research and development (R&D) model is no longer viable, and drug companies are evolving their approach. Rather than only pursue blockbuster therapeutics for heterogeneous, common diseases, drug companies have increasingly begun to shift their focus to rare diseases. In academia, advances in genetics analyses and disease mechanisms have allowed scientific understanding to mature, but the lack of funding and translational capability severely limits the rare disease research that leads to clinical trials.

Although each rare disease affects less than 200,000 individuals in the United States, in aggregate, rare diseases affect 6-7% of the population. According to the National Organization for Rare Disorders (NORD), there are only 250 treatments for the nearly 7,000 rare disorders, impacting nearly 30 million Americans. Eighty percent of these diseases have a genetic origin.

Orphan drugs are designed to treat some of the rarest medical conditions known to humans. According to the NIH, there are about 7,000 rare diseases that fit this definition, including cystic fibrosis, amyotrophic lateral sclerosis, Duchene muscular dystrophy, and Gaucher's disease. The cost of developing orphan drugs can be prohibitive for most companies in the biotechnology and pharmaceutical sectors, especially without any incentives from the regulators. In order to encourage research into developing orphan drugs within its borders, United States enacted the US Orphan Drug Act in 1983, which introduced a number of incentives designed to increase their development.

Objectives

The objectives of the present study are

1. To compare the pre and post product development situation of rare diseases
2. To know the clinical phases (I-IV) of product development for rare diseases

History of Orphan Drugs in United States

By the time the Orphan Drug Act (ODA) was introduced in December 1981, Congress was increasingly concerned by the lack of orphan drug development. Growing public awareness led to a series of Congressional hearings in the early 1980s that focused on the barriers hindering orphan drug development. Congress intended the ODA to help drug developers overcome these barriers and encourage innovation in the treatment of rare diseases. Over time Congress has amended the ODA to further combat barriers to orphan drug development. For example, in 1992, the ODA was amended to include FDA user fee waivers for orphan drug developers, and in 1997, the Orphan Drug Tax Credit (ODTC) was permanently extended. Appendix B highlights some of the key Congressional and other activities related to orphan drugs in the United States. Since the ODA, other initiatives have promoted additional progress in the treatment of rare diseases. In 2002, legislation created what is today called the Office of Rare Disease Research within the National Institutes of Health (NIH) to coordinate research on treatments for rare diseases. As part of the FDA, the Office of Orphan Products Development (OOPD) oversees the provisions contained in the ODA and administers the Orphan Products Grant Program, which awards approximately $14 million each fiscal year in research grants aimed at supporting orphan drug research. Today, many different networks and organizations, such as the National Organization for Rare Disorders (NORD), help facilitate research and patient support in the United States and other countries.

The Orphan Drug Stimulus[2]

The Food and Drug Administration has charged The Office of Orphan Products Development (OOPD) to dedicate its mission to promote the development of products that demonstrate promise for the diagnosis and/or treatment of rare diseases or conditions. It administers the major provisions of the ODA, which provide incentives for sponsors to develop products for rare diseases. The ODA has been very successful in foster the

developing of more than 200 drugs and biological products for rare diseases which have been brought to market since 1983. In contrast, the decade prior to 1983 saw fewer than ten such products in market. In addition, the OOPD administers the Orphan Products Grants Program which provides funding for clinical research in rare diseases. The FDA funds the development of orphan products through its grants program for clinical studies. The Request for Applications (RFA) announcing availability of funds is published in the Federal Register each year – usually in June.

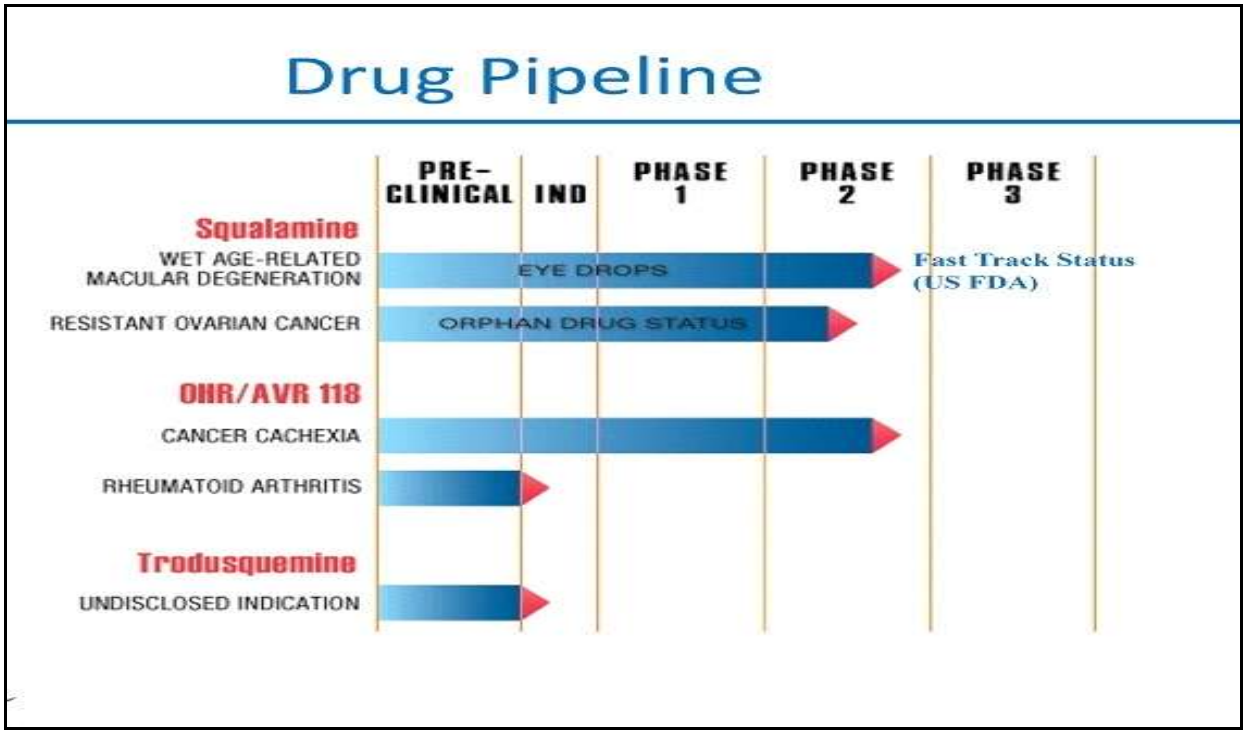

Figure 1: Orphan drug pipeline

Challenges in Access to and Affordability of Medicines for Rare Diseases

Despite the progress, no effective and safe treatment is available for many rare diseases. Furthermore, when treatments are available, obstacles are encountered that hinder access and use of these drugs.

Lack of knowledge and training

For many rare diseases, available information is inadequate. Health professionals are often deficient in appropriate training and awareness to be able to diagnose and adequately treat these diseases.

Deficient diagnostic systems

For many diseases, no diagnostic methods exist, or diagnostic facilities are unavailable. In these cases, diagnosis may be problematic. Consequently, validity, coding, and reproducibility are problems. Although the pace of gene discovery for rare genetic diseases has accelerated during the past decade, in part, due to the success of the Human Genome Project, translation of these discoveries to clinical utility still lags behind.

High prices

Prices of orphan drugs per treatment episode can be very high. For example, the cost of treatment with enzyme replacement therapies may reach more than US$150,000 per treatment year. The affordability of orphan drugs has become a major issue for players and is thus a strong driver of tensions between the different stakeholders. Some companies have responded to this by developing programs to facilitate access to orphan drugs.

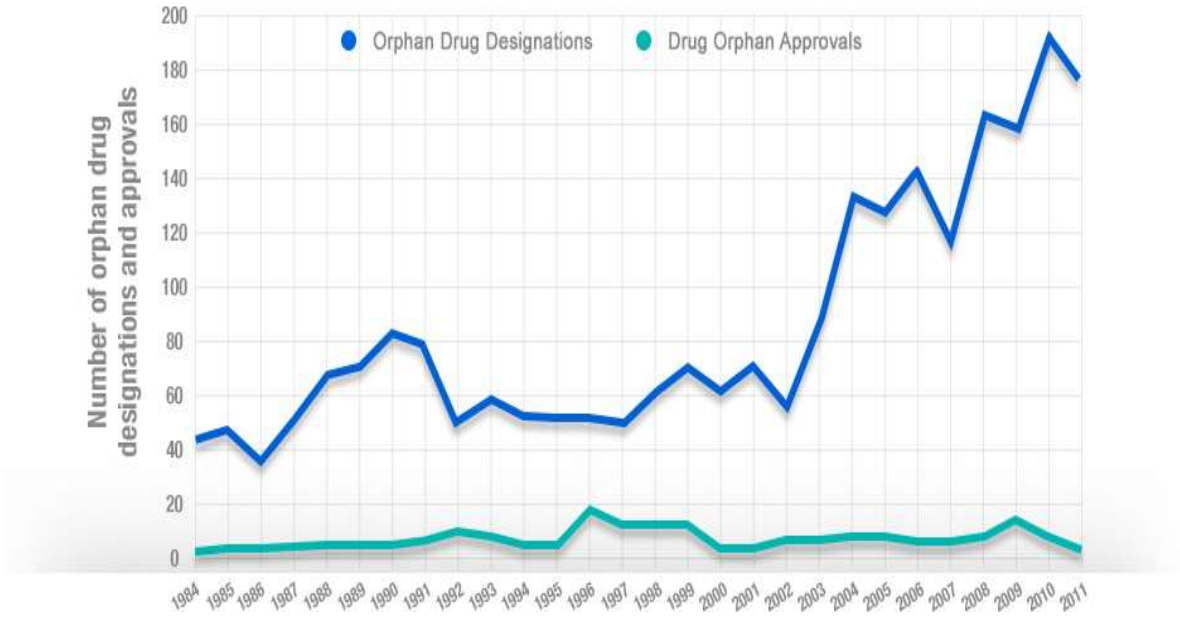

Figure 2: New Orphan Drug Designations Climb: Approvals don't keep pace

Role of Pharma industry

The growth of pharma industries has slowed in recent years because of various reasons such as patent expiries, generic competition, drying pipelines, and increasingly stringent regulatory guidelines. Many blockbuster drugs will lose their exclusivity in next 5 years. Therefore, the current economic situation plus the huge generic competition shifted the focus of pharmaceutical companies from the essential medicines to the new business model — niche busters, also called orphan drugs. Orphan drugs may help pharma companies to reduce the impact of revenue loss caused by patent expiries of blockbuster drugs. The new business model of orphan drugs could offer an integrated healthcare solution that enables pharma companies to develop newer areas of therapeutics, diagnosis, treatment, monitoring, and patient support. Incentives for drug development provided by governments, as well as support from the FDA and EU Commission in special protocols are a further boost for the companies developing orphan drugs. Although there may still be challenges ahead for the pharmaceutical industry, orphan drugs seem to offer the key to recovery and stability within the market.

Regulatory and Scientific Characteristics of Orphan Drugs[3]

In the entire group of approved orphan drugs, among the 248 orphan products for which data could be found on the FDA website, there were 164 (66 percent) products for which the original FDA approval date coincided with the initiation of their orphan drug market exclusivity, meaning that their original approval in the United States was for an orphan indication. The remaining 84 (34 percent) had all been approved by the FDA for another indication prior to their orphan drug designation. To cull more information about the inventiveness, regulatory histories, and other clinical uses of drugs approved with orphan designations, full medical reviews from the NDA were available from the FDA website for 81 of the 101 drugs approved with orphan designations from 2000 to 2009.Additional information, including the current drug label, was available from the FDA website for all products, except nine clotting factors, approved during this time.

Among the drugs in this subset, 34 met the study definition of "new" (34 percent). Such drugs included those approved as a New Molecular Entity that had not previously been available in the world before the current regulatory submission.

Another 36 (36 percent) were adaptations of or related to prior-approved drugs. Seventeen (47 percent) of these drugs involved changes in method of administration. The remaining 19 (53 percent) drugs were members of the same class as previously approved product.

Finally, there were 31 drugs (31 percent) that had previously been approved in the United States or elsewhere. Thirteen of the 31 old drugs (42 percent) were available in the United States at the time of their

orphan drug approval. For example, raloxifene (Evista), approved in 2007 to reduce the risk of invasive breast cancer in certain high-risk post-menopausal women was approved in 1997 for the prevention of osteoporosis in post-menopausal women. Twenty-seven of the 31 drugs (87 percent) were previously available overseas or Canada.

Clinical Trials

Preclinical development[4]

Once a single promising compound is selected based on the kinds of basic research and therapeutic discovery which was reviewed, companies initiate preclinical studies both *in vitro* and in animals to evaluate a drug's safety and potential toxicity. These preclinical studies are also used to assess potential effectiveness. Sponsors design additional studies to provide convincing evidence that a drug is not mutagenic (i.e., it does not cause genetic alterations) or teratogenic (i.e., it does not cause fetal malformations).Because a patient's ability to excrete a drug can be just as important as the patient's ability to absorb the drug. The safety and other data from preclinical studies are crucial in determining whether a drug will move on to studies in humans. Preclinical studies also guide researchers in designing phase I clinical trials. They also help to identify criteria for evaluating safety in humans, including signs and symptoms that should be monitored closely during early clinical trials.

Researchers can also use specifications assigned in the preclinical stage to evaluate the chemical quality and purity of the drug, its stability, and the reproducibility of the quality and purity during repeat manufacturing procedures. (This is sometimes referred to as "chemistry, manufacturing, and controls [CMC] information." CMC requirements and CMC activities evolve during the entire development process. The FDA repurposing initiative described below emphasizes the value of this preclinical work if sponsors see a possible new use of an already-approved drug for a rare disease.

Preclinical studies, as well as manufacture of the drug at small scale, can be very expensive (several million dollars) and time-consuming (1 to 2 years). These studies also require specific expertise, both in the proper design and execution of the studies and in the proper interpretation of the results. Most studies need to be done under good laboratory practice (GLP) conditions to qualify for regulatory submission (21 CFR Part 58). GLP conditions apply not only to specified instrumentation, record keeping, and analysis, but also to specific laboratory conditions that, in most cases, require special facilities.

By their very nature, studies in preclinical development are major hurdles in the development of therapeutics for all diseases—but especially those that are rare.

There are several clinical trial phases that are conventionally used to develop evidence of safety and efficacy for drugs intended for common conditions. For drugs intended for quite rare diseases, the delineation among phases I, II, and III trials is often not as clear. The agency strongly encourages sponsors of drugs for rare diseases to seek meetings with FDA to discuss development strategy prior to submission of an Investigational New Drug (IND) application.

Phase-I:clinical trial: safety[5]

Before clinical studies can begin, sponsors must submit an IND application to FDA. This application must include the results of the preclinical studies. Given the generally small numbers of patients available for the study of rare diseases, sponsors benefit particularly from regulatory guidance on the extent of phase I analysis that CDER considers sufficient prior to the start of phase II clinical trials.

Phase I trials initiate the testing of drugs in humans. They often involve small numbers (20 to 100) of healthy volunteers but sometimes include research participants with a rare or other specific condition for which targeted pathways have been identified as potentially relevant to disease pathogenesis. A phase I study may last for several months. Drug doses usually start at very low levels, and research participants are monitored very carefully as the dose is escalated.

Phase I studies focus on the evaluation of a new drug's safety, the determination of a safe dosage range, the understanding of the drug's clinical pharmacology, the identification of side effects, and sometimes the

detection of early evidence of effectiveness if the drug is studied in patients with the target disease. From phase I clinical trials, researchers gain important information about

- the drug's effect;
- the drug's pharmacokinetics (absorption, distribution, metabolism, and excretion) to better understand a drug's properties in the body;
- the acceptability of the drug's balance of potency, pharmacokinetic properties, and toxicity or the specificity of the drug (i.e., its ability to hit its desired target without altering another biological process); and
- The tolerated dose range of the drug.

In January 2006, CDER issued guidance on exploratory IND studies (CDER, 2006). It defined such studies (which some refer to as phase 0 clinical studies) as occurring early in the initial phase of clinical studies, having no diagnostic or therapeutic purposes, and involving very limited exposure of humans to the investigational drug. The guidance urged sponsors to consider exploratory IND studies, in particular, for drugs intended for patients with serious, life-threatening diseases, which is often the case for rare diseases. Such studies involve fewer resources than conventional approaches and thus allow sponsors to "move ahead efficiently with the development of promising candidates". For example, during such an exploratory study, sponsors can test one or more related compounds at very low doses that are sufficient to determine the half-life, absorption, metabolism, and excretion of a drug.

The guidance on exploratory IND studies is relatively recent. Such studies will occur long before an application for approval reaches FDA, so it will take time before the effect of this approach on product development for rare conditions can be assessed.

Phase-II: Clinical trials: Efficacy

In conventional clinical trials for drugs for common conditions, phase II studies provide an investigational drug's first test of efficacy in research participants who have the disease or the condition targeted by the medication. Even if combined phase I-II trials are performed to obtain initial findings of safety and efficacy, larger phase II trials will normally be needed to determine optimal dosing to maximize efficacy and minimize adverse events. These studies may include up to several hundred participants and may last from several months to a few years.

For drugs which are intended for rare conditions, FDA may accept studies involving smaller numbers of research participants than are required for more common conditions. It may also allow the use of historical controls (or possibly no controls) if the rare disease has a defined course in the absence of treatment that will permit comparisons with results for an investigational drug.

Phase II studies help determine the correct dosage, identify common short-term side effects, and define the best regimen to be used in pivotal clinical trials. Conventionally, the initial step is usually a phase IIa clinical trial that is focused on an initial proof of concept. This step is to demonstrate that the drug did what it was intended to do: that is, it interacted correctly with its molecular target and, in turn, altered the disease. Phases I and IIa are sometimes referred to as "exploratory development." Phase IIb trials are larger and may use comparator agents and broader dosages to obtain a much more robust proof of concept and additional guidance on dose selection. They are often done at a regulatory standard that requires conformance with good clinical practice principles and guidelines.

Phase-III: Clinical trial: Regulatory proof[6]

Conventional phase III clinical trials are designed to evaluate a candidate drug's benefit in a carefully selected patient population with the disease. These trials are to confirm efficacy, further evaluate safety and monitor side effects, and sometimes compare the candidate drug to commonly used treatments. They provide crucial evidence needed to satisfy regulators that the drug meets the legal requirements for marketing approval and to provide necessary information for product labeling after approval of the drug.

For common conditions, phase III studies are usually conducted with large populations consisting of several hundred to several thousand participants who have the disease or the condition of interest. Phase

III trials typically take place over several years and at multiple clinical centers around the world. The study drug may be compared with existing treatments or a placebo. Phase III trials are, ideally, double blinded; that is, neither the patient nor the investigator knows which participants are receiving the drug and which are receiving existing treatment or placebo during the course of the trial.

FDA typically requires two phase III clinical trials for approval of a drug, but the law authorizes FDA to approve a drug based on one multi-center study in appropriate circumstances. Because the number of patients available to participate in a clinical trial involving a rare disease is often very small, FDA frequently approves orphan drugs with less extensive requirements for clinical studies.

If clinical trials are successful, a New Drug Application (NDA) is submitted to FDA for review. The review process usually takes 10 to 12 months and may include, at the discretion of FDA, an advisory committee review. Drugs for rare conditions may qualify for one of several options for speeding the path to approval.

Phase II, and sometimes phase III, trials may fail due to the large heterogeneity of the patient population being studied. As a result of genetic heterogeneity, some research participants may respond well and others may not respond at all to an investigational product. Because most rare diseases have a more homogeneous genetic pattern than do common diseases and because they are often characterized by similar or identical genetic or epigenetic defects, patients with these diseases could be expected to have a more uniform response to a drug. This should reduce the size of phase II and III studies required to demonstrate efficacy.

Phase-IV: Post-Market Surveillance

FDA will frequently specify post-marketing study (phase IV) requirements to further evaluate an approved drug and obtain more information about safety or effectiveness or both. Such studies are required if the accelerated approval process is used. Approval for one drug (not for a rare disease) was recently rescinded based on post-marketing study results that indicated no benefit. Many of the approvals of drugs for rare diseases reviewed by the committee included provisions for various kinds of post-marketing studies.

Roles of CDER in Orphan Drug Approval

As is the case for other drugs, CDER is responsible for reviewing and approving NDA applications for orphan drugs. In general, the review divisions of CDER are organized around therapeutic areas such as neurology and gastroenterology.

Recently, FDA announced the creation of a new position within CDER, the Associate Director for Rare Diseases, who will serve as the center's lead person on issues involving orphan drugs and rare diseases. Responsibilities will include

- serving as the primary contact for the rare diseases community,
- assisting developers of drug and biologic products in understanding and following relevant regulatory requirements,
- coordinating the development of policies within CDER for the review an approval of drugs for rare conditions, and
- Encouraging collaboration among CDER scientists and clinician

ANALYSIS[7]

This review of the regulatory and scientific characteristics of drugs developed under the Orphan Drug Act involved three different subsets of orphan drugs. The first subset was the full list of orphan drugs approved from 1983 to 2009. While there were a total of 347 approvals, those approvals included 279 separate drugs. Among that sample, the vast majority of drugs were approved only for a single orphan condition (most likely in the field of oncology).

The second subset was the 101 orphan drugs approved from 2000 to 2009; in this sample, more details of the drugs' regulatory history and scientific context of their approval were assessed. The sample was roughly evenly divided among “new” drugs, drugs already available in the United States or abroad, and variations of

previous drugs, although the numbers of old drugs and drug variations approved as orphan drugs increased over the time period.

The final subset consisted of the 30 products approved from 2007 to 2009 where full FDA medical officer reviews were available; in this sample, the clinical trial development process was analyzed. The results showed that clinical trial development took about 6 years, with official orphan drug designation occurring toward the end of the development.

Source for rare diseases (National Institutes of Health)[8]

Just as pharmaceutical companies have had reasons to innovate, NIH has, in recent years, been called upon to complement its support for basic biomedical discovery by facilitating the translation of discoveries into therapies for both common and rare diseases. It too is building "innovation platforms" to support such translation.

As part of its Roadmap initiative, NIH launched the Rapid Access to Interventional Development (RAID) program as a pilot activity in 2004. Not a grant program, RAID supports selected aspects of preclinical development, providing expertise and performing required studies at a regulatory level using existing NIH facilities and contract resources. Academic investigators as well as qualified small businesses are eligible to use the resource.

Market Exclusivity and Patents[9]

The incentives provided by market exclusivity for orphan drugs need to be understood in the context of both patent law and other policies granting exclusivity for drug sponsors. Patent law provides an important means for innovators to protect their inventions or intellectual property from competitors. It gives patent holders the exclusive right to produce, use, or sell the patented invention for a specified period. Patents are issued by the U.S. Patent and Trademark Office and, under current law, extend for 20 years from the date of submission of the patent application.

By the early 1980s, the research and development process for new drugs combined with the time required for FDA review had reduced the effective patent life for the average new drug to well below the 17 years then available under patent law. In the Drug Price Competition and Patent Term Restoration Act of 1984, (widely known as the Hatch-Waxman Act), Congress provided for the restoration of a portion of the patent term consumed by clinical studies and FDA review. In general, patent term restoration is limited to 5 years and an effective period of (post approval) patent protection of 14 years.

The first exclusivity rule provides that truly innovative drugs—new chemical entities (also called new molecular entities)—receive a 5-year period of data exclusivity, during which the sponsor of a generic drug must submit a full New Drug Application that relies on its own preclinical and clinical data. At the end of 5 years (4 years if the generic drug applicant chooses to challenge the innovator's patents), the applicant can submit an ANDA that need only show that its product is the same as, and bioequivalent to, the innovator's product.

The second exclusivity rule provides that other applications for approval that are supported by clinical data (e.g., those involving new formulations of the drug) receive 3 years of exclusivity. Again, during the period of exclusivity, generic versions can be approved only if sponsors provide their own clinical data on safety and efficacy.

In 1997, Congress enacted the Best Pharmaceuticals for Children Act (as part of the FDAModernization Act) to encourage the testing of pharmaceuticals for children. If a company conducts pediatric studies in response to a written request from FDA and complies with various requirements relating to these studies, the law provides for an extension of 6 months to the exclusivity periods described above.[10]

The market exclusivity incentive for orphan drugs is broader than the various types of exclusivity which are discussed. During the period of exclusivity, FDA *cannot* approve an application from a different manufacturer for the same orphan drug and the same indication-even if that sponsor provides independent clinical data of safety and efficacy.

The approval of an application for orphan designation is based upon the information submitted by the sponsor. A drug that has obtained orphan designation is said to have "orphan status."

The Future of 'Orphan Drug'[11-13]

Rare diseases need more attention due to lack of proper diagnosis and treatment. Treatment and prevention for rare diseases is considered as "no man's land." The EU parliament should provide more benefits like tax incentive, special status, and reimbursement for these orphan drugs. This encouragement can bring in a revolution among the pharmaceutical and biotechnology companies for developing and marketing orphan drugs. EURODIS and other organizations are creating awareness on rare diseases and are also influencing governments in bringing legislation acts for better quality of life for these special people. EURORDIS and National Alliances have announced "rare day" on February 29th and dedicated this day to special people who are affected by rare diseases. Henceforth, 29th February will be called "the rare disease day."

The future of the orphan drug industry will depend heavily upon the entry of bio generics, since biologics account for over 50% of the orphan drug market. It can be expected that the orphan drug market growth will remain positive as more and more governments are taking action to promote this sector, especially in Asia.

The issue of orphan drugs becomes more important for third world countries like India. Usually we criticize the pharmaceutical industry or manufacturers for this. The manufacturers of drugs have to amortize their operational expenses, their research investment, and still make reasonable profit so that they can finance new ventures in the future. It is calculated that return on investment for the average new chemical entity (NCE) is barely 6-8%, a figure with serious implications for a prudent businessman. One area where the ODA has not provided very strong incentives is new drugs and vaccines. However, developing countries lack the resources to afford these drugs, with many devoting as little as $2 per capita per year to heath care. Also Research and Development costs have been rising and drug prices declining.

A country should try to produce important drugs for the benefit of the whole world, depending on the R and D investment, the return on such investment, the tax and patent incentives, and its regulatory policies. Agreement of these points might lead to beneficial changes in our national thinking and prevent "orphanization of new drugs."

Summary & Conclusion

In the past decades, there were only few products developed for rare diseases by pharmaceutical companies, since rare diseases affect small population. Rare diseases need more attention due to lack of proper diagnosis and treatment; the return on investment by pharmaceutical organizations was not high. In order to boost the development of products, FDA has initiated funding (grants) for rare diseases. In the recent past, there has been development in drug approvals for orphan and rare diseases. USFDA has awarded 18 new research grants totalling more than $19 million to boost development of products for patients with rare diseases. The grants will trigger the orphan drug/ rare disease pipeline, which may be a ray of hope for patients with orphan and rare diseases.

Table 1: The grant recipients for fiscal year 2015

Recipient	***Study***	***Treatment***	***Population***
Albert Einstein College of Medicine (Bronx, New York), Deepa Manwani	Phase 2 Study of Gamunex	Treatment of Sickle Cell Acute Pain	About $1.6 million over four years
Baylor College of Medicine (Houston, Texas), Andrew Sikora	Phase 2 Study of ADXS11-001 Vaccine	Treatment of HPV-Related Oropharyngeal Cancer	About $1.2 million over 3years
Beckman Research Institute of the City of Hope (Duarte, California),	Phase 1 Study of Cellular Immunotherapy Using Optimized	Treatment of Malignant Glioma	About $600,000 over three years

Behnam Badie	IL13Ra2 Specific CAR T Cells		
Columbia University (New York, New York), Suzanne Lentzsch	Phase 1A/B Study of 11-1F4 mAb	Treatment of AL Amyloidosis	About $600,000 over three years
Edimer Pharmaceuticals Inc.(Cambridge, Massachusetts), Neil Kirby	Phase 2 Study of EDI200	Treatment of X-Linked Hypohidrotic Ectodermal Dysplasia	About$1.6 million over 4 years
Emory University (Atlanta, Georgia), Claudia Morris	Phase 2 Study of L-Arginine Therapy	Treatment of Pediatric Sickle Cell Disease Pain	About$1.6 million over four years
Indiana University-Purdue University at Indianapolis (Indianapolis, Indiana), Kent Robertson	Phase 2 Study of Imatinib for the Type 1	Treatment of Airway Tumors in Children with Neurofibromatosis	About$1.6 million over four years
Indiana University-Purdue University at Indianapolis (Indianapolis, Indiana), Sharon Moe	Phase 1 Study of Low Dose Pioglitazone	Treatment of Autosomal Dominant Polycystic Kidney Disease	About $600,000 over three years
New York University School of Medicine (New York, New York), Horacio Kaufmann,	Phase 2 Study of Carbidopa	Treatment of Familial Dysautonomia	About$1.1 million over 3y
Northshore University Health system (Evanston, Illinois), Eli Ehrenpreis,	Phase 1 Study of Naltrexone	Treatment of Mesenteric Panniculitis	About $220,000 over three years
Rhythm Metabolic Inc. (Boston, Massachusetts), Keith Gottesdiener	Phase 2 Study of the Melanocortin 4 Receptor Agonist RM-493	Treatment of Prader Willi Syndrome	About$1 million over three years
University of Michigan (Ann Arbor, Michigan), Meghan Arnold	Phase 3 Study of Standard vs Reduced IV Fat	Prevention of Parenteral Nutrition-Associated Cholestasis (PNAC)	About$1.6 million over four years.

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