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Rare Diseases of the Eye — Development Opportunities for Novel Therapies

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Executive Summary

In part one of this rare disease whitepaper series, Dr. Jonca Bull provides an overview of orphan drug development, discusses the unique challenges associated with developing therapies for rare eye disorders and provides information on PPD's patient-centric strategies to overcome these challenges.

Developing therapies for rare ophthalmologic disorders present a range of unique challenges — from disease characterization and determination of appropriate endpoints to trial design, patient recruitment and site selection. Advances in science, extending from genomics to real-world evidence, offer unprecedented opportunities to explore innovative research strategies that can achieve clinical trial success. This paper discusses key concerns and success factors in developing therapies for rare diseases of the eye, with a focus on PPD's capabilities to meet the special challenges of the patient-centered rare disease research environment.

Renaissance in Rare Disease Research

The modern era of rare disease research begins with a mother and a sick child. Abbey Meyers, founder of the National Organization of Rare Disorders (NORD), explained it this way:

"I said to myself, 'I'm fighting this because of one little kid, who happens to be my son, but this can't possibly be a problem just for my family.' So I called up the support of groups for other rare diseases — Huntington's scleroderma, and so on — and I asked, 'Are you having this problem too?' and most of them said yes. And I realized that, if somebody did find a cure for one of these diseases, it was never going to be manufactured."[1]

Over the past 25 years, patient advocacy (now powered by social media), advances in genomic sciences, and regulatory incentives have combined to forge a framework that is making progress in delivering new therapies to address more than 7,000 identified rare diseases — 90 percent of which currently lack specific treatments.[2]

Since enactment of the of the Orphan Drug Act in 1983, the U.S. Food and Drug Administration (FDA) has approved more than 400 rare disease therapies, compared to fewer than 10 introductions in the decade before.[3] In 2015 and again in 2016 and 2017, rare disease indications accounted for more than 40 percent of the FDA's new drug approvals.

Science-driven Opportunities; Regulatory-driven Incentives

The renaissance in rare disease research has been fostered by orphan drug regulations that provide marketing incentives and streamline approval pathways for therapies whose intended patient populations are often too small to deliver sufficient return on development investment. A rare disease is defined in the United States as one affecting fewer than 200,000 people, and in the European Union (EU) the prevalence must be below five per 10,000 of the EU population.[3]

The FDA grants seven years of market exclusivity for drugs that earn orphan designation under the Orphan Drug Act; the European Medicines Agency (EMA) grants 10 years of exclusivity for drugs that earn the EMA's Orphan Designation. Both agencies support flexible, innovative clinical research approaches and offer a common application pathway for FDA/EMA orphan medicinal product designations.

These incentives have spurred translation of genetic knowledge into therapeutic applications. An estimated 80 percent of known rare diseases are genetic in origin, and children account for approximately 50 percent of rare disease populations.[6] The explosion of knowledge in genomics is yielding a rich development pipeline that now holds an estimated 560 agents targeted for rare disease conditions.[7]

Bringing these advances to patients demands novel research approaches in study design, trial operations and patient recruitment, all of which depend upon keeping the patient at the center of the research process.

Progress in Rare Diseases of the Eye

Genetics and potential gene therapies are revolutionizing the understanding of rare ophthalmic diseases, giving drug developers unprecedented opportunities to advance therapeutics in this field of largely unmet medical need.

Diseases of the eye can be progressive, chronic and incurable, leading to visual impairment and blindness if not adequately treated. The major ophthalmic diseases are glaucoma, age-related macular degeneration (AMD), diabetic macular edema and diabetic retinopathy. Treatment focuses on disease management to reduce the severity of symptoms and slow progression.

Figure 1. Orphan Eye Disease designations that led to approved products 1983-present

	Indication	Date of Designation	Approval
Ofloxacin	Treatment of bacterial corneal ulcers	4/18/1991	1993
Gangciclovir Intravitreal Implant	Treatment of CMV	6/7/1995	3/4/1996
Cysteamine hydrochloride	Treatment of corneal cystine accumulation in cystinosis patients	8/9/1997	10/2/2012
Dexamethasone intravitreal implant	Treatment of non-infectious ocular inflammation of the posterior segment in patients with intermediate, posterior, and panuveitis	9/11/1998	6/17/2009
Fluocinolone	Treatment of uveitis involving the posterior segment of the eye	7/31/2000	11/4/2004
Trypan Blue	Selectively staining epiretinal membranes during ophthalmic surgical vitrectomy procedures	8/2/2006	12/16/2004
Mitomycin C	Treatment of refractory glaucoma as an adjunct to ab externo glaucoma surgery	1/08/2008	2/7/2012
Difluprednate	Treatment of endogenous and traumatic anterior uveitis and panuveitis	9/30/2008	06/23/2008
Riboflavin ophthalmic solution UVA radiation	Treatment of corneal ectasis following refractive surgery	12/2/2011	04/15/2016
Adalimumab	Treatment of non-infectious intermediate, posterior, or panuveitis,or chronic non-infectious anterior uveitis	5/13/2014	6/30/2016
Voretigene neparvovec-rzyl	Treatment of inherited retinal dystrophy due to biallelic RPE65 gene mutation	03/18/2015	12/19/2017

The National Institutes of Health estimates that there are more than 550 rare ophthalmic diseases, based on the medical literature and other research. These include diseases with eye and orbital deformities and systemic findings related to retinal dystrophies.[8] A critical concern is that rare diseases of the eye predominantly affect children and have a significant impact on their development and potential for a productive life. Examples include retinitis pigmentosa, Stargardt's disease and Leber congenital amaurosis.

Since 1983, FDA has granted 10 orphan eye disease designations that have resulted in approved products (Figure 1). We expect to see these numbers increase as scientific advances drive new approaches, including gene therapy, neuroprotection and other novel therapies.

Regulatory policies and programs that support orphan drug development — breakthrough and fast-track designations, priority review and accelerated approval — have played an important role in bringing these therapies to patients.

Especially important is the flexibility written into regulations to enable drug developers to implement innovative designs and methodologies for clinical evaluation in small rare disease populations. According to a NORD study, 90 of the 135 orphan drug approvals reviewed between 1983 and 2010 (67 percent) resulted from some exercise of FDA flexibility in applying the statutory standard for evidence of effectiveness.[9]

Current Rare Eye Disease Research

As demonstrated in databases for orphan designations, the more commonly researched rare populations are retinal dystrophies, uveitis and corneal ulcers.

Research is also evolving to a greater focus on novel indications for the rare and ultra-rare populations in conditions such as Leber congenital amaurosis and achromatopsia. Traditional site-based trials are not feasible in most cases due to very small, geographically dispersed patient populations. New approaches in clinical evaluation show increased reliance on patient-centric study designs that collect data remotely via internet-based and mobile health technologies, including telemedicine, intelligent devices and wearable sensors. These technologies bring the study to the patient, allowing them to participate from home, regardless of geographical location and without interrupting their everyday activities and support networks.[10]

Another approach using precision medicine focuses on "rare-like" patient populations — that is, small subsets of more prevalent eye disease populations — in AMD and geographic atrophy. With the expansion of precision (targeted) medicine, increasing

numbers of subset populations are being identified based on targetable genetic characteristics.

Identification of subset populations is the fastest growing strategy in rare ophthalmologic disease research. In addition to the challenges posed by patient recruitment and site-based operations, evaluation of targeted therapies requires expertise in genetics and supporting operational capabilities for DNA sampling, analysis and storage. Logistical support for these trials can be a major hurdle for drug developers.

Challenges in a Changing Research Paradigm

The current research landscape in rare ophthalmic diseases points to the key challenges in rare disease drug development: finding scarce patients, insufficient knowledge of the natural history of a targeted disease, and the need to address rapidly evolving genetic knowledge as it relates to patient populations.

The success of clinical trials depends heavily on effective solutions to identify, locate and enroll patients. In addition to the patients known to highly specialized ophthalmic investigators, social media has become a highly effective research tool for locating and recruiting rare disease patients who rely on internet communications to share information and support.

Development of effective interventions requires understanding of disease progression — from the time immediately prior to inception through pre-symptomatic and clinical treatment stages, and ultimately to an outcome in the absence of treatment. Genetic analytics and the ability to characterize at-risk populations impacts patient selection and trial design — for example, in the case of an X-linked rare disease where male patients predominate.

Operationally, the central challenge to successful clinical evaluation is identifying appropriate populations, locating the identified patients, and recruiting and retaining sufficient numbers to conduct a trial. Rare disease populations are small and widely dispersed. Site-based trials can require a large number of sites spread across multiple regulatory jurisdictions with each enrolling only a few subjects.

Rare diseases also pose significant challenges for study design. Endpoints to serve as appropriate measures for disease assessment often are not established, which makes protocol development difficult. There are often late changes to planned approaches and methodologies, especially if regulatory consultation is still underway. A low number of patients can make data more difficult to interpret when writing clinical study reports (CSRs).

Looking Ahead

An evolving framework of scientific and regulatory tools is emerging to support the design and implementation of successful development programs. Genomic testing, leveraged by increasing knowledge of disease natural history, is being used to characterize relevant patient populations. In clinical evaluation, a major focus is the determination of clinical endpoints that have impact and relevance to patients' quality of life. And patient experience — assessed using both objective and subjective measures — is being incorporated into study design and protocols.

GARD and eyeGENE head a growing list of valuable resources for drug developers. GARD, the Genetic and Rare Diseases Information Center, is a collaboration of the National Center for Advancing Translational Sciences (NCATS) and the National Human Genome Research Institute (NHGRI). The online GARD database provides accurate, updated information on current rare disease research, symptoms and interventions.[11] eyeGENE® is the National Eye Institute's National Ophthalmic Disease Genotyping and Phenotpying Network, which facilitates research in the genetic causes and mechanisms of rare inherited eye diseases.[12]

Success in Action: Potential First Gene Therapy for Inherited Rare Eye Disease

In October 2017, an FDA advisory committee unanimously endorsed the first true gene therapy for an inherited disorder, Spark Therapeutics' Luxturna®. Luxturna delivers a healthy version of the RPE65 gene — injected into the eye — to produce a protein essential for sight in patients born with defective copies of RPE65. Mutations of RPE65 cause inherited retinal diseases, such as Leber congenital amaurosis or retinitis pigmentosa, which affect an estimated 1,000 to 2,000 U.S. patients. Vision gets progressively worse, resulting in night blindness, loss of peripheral and central vision, then blindness. Children treated with Luxturna reported seeing rain and snow for the first time and a 24-year-old woman who said she was "living in a black-and-white film" suddenly could see vibrant colors.[13]

Essential to the development of this breakthrough therapy was the use of an innovative endpoint — the multi-luminance mobility test. Traditional ophthalmic evaluations measure how the eyes perform using tests of visual acuity, visual field and contrast sensitivity. The multi-luminance mobility test measures how the person performs in vision-related functions, such as reading, or moving through a room or outdoor space. The test assesses the person's ability to perform tasks in light levels ranging from a "moonless summer night or indoor nightlight (1 lux)" to an "office environment or food court (400 lux)."

Designing endpoints that are both clinically relevant and meaningful to patients in the context of their sight-limiting disease helps define research objectives in terms of benefits. Perceived benefits, in turn, drive other vital success factors, including investigators' enthusiasm for conducting trials and patients' willingness to participate.

Key Strategies for Patient-centric Rare Disease Trials: PPD's Solutions

Patient engagement is the most important factor in the success of rare disease studies. Three primary considerations are:

- Giving patients a voice in protocol design: addressing the patient perspective on potential benefits and risks
- Communicating and connecting with patients to build strong site-patient relationships aimed at patient retention and positive research experience
- Optimizing convenience for patients and families: considering home-based operations, including endpoint data collection, and providing transportation services or streamlining on-site activities

PPD has more than 20 years of experience conducting global ophthalmology clinical trials. In the past five years, our experience has spanned 71 ophthalmology studies in nearly 24,000 patients with 16 of these trials in rare ophthalmic diseases and involved more than 1,000 patients enrolled in more than 300 sites worldwide.

PPD's specialized rare disease approach incorporates patient and caregiver input to study design and includes approaches that use remote data capture to minimize patient travel. PPD's Rare Disease and Pediatric Center of Excellence is a dedicated leadership team that develops solutions to addresses strategic, scientific and operational challenges of rare disease trials. The center of excellence team drives all of PPD's rare disease and pediatric activities with accountabilities that span all therapeutic areas. Our expanding longitudinal site relationships include PPD's Pediatric Investigator Network, a network of 14 global pediatric centers of excellence established to accelerate and optimize the development of therapies specifically for pediatric populations.

Figure 2. PPD's Rare Disease Research Framework

New Initiatives Drive a Bright Future

Rare diseases now represent the fastest growing sector of pharmaceutical and biotechnology drug development, thanks to advancing genomic sciences, innovative research approaches and regulatory incentives. The FDA's Office of Orphan Products Development (OOPD) received 568 new requests for orphan designations in 2016 — more than double the requests in 2012.[14]

New regulatory initiatives will drive expansion of rare disease research in two directions. In 2016, OOPD launched the Orphan Products Natural History Grants Program and provided approximately $2 million in grants that supported natural history studies in 2017 to better understand disease progression, an essential foundation for therapeutic development.[15] In June 2017, the FDA announced the Orphan Drug Modernization Plan to speed review and eliminate backlog of the increasing number of orphan designation requests.

The most important trends to advance treatment for rare diseases of the eye are advances in genomics and gene therapy. There is unprecedented potential both to characterize the underlying genetic defect and to design a therapy that can impact progression or even cure.

Building on these breakthroughs, PPD will continue to advance its capabilities to meet the challenges for rare disease clinical trials. These include driving innovations for patient engagement and operational efficiencies to speed important new therapies to market.

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