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BY ELECTRONIC SUBMISSION

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane
Room 1061, HFA-305
Rockville, MD 20852

RE: Docket No. FDA-2019-N-0077-0001; Patient Perspectives on the Impact of Rare Diseases: Bridging the Commonalities; Public Meeting

Dear Dr. Maynard and Ms. Furia-Helms:

On March 1, 2019, the Food and Drug Administration ("FDA" or "the Agency") issued a notice announcing a public meeting entitled "Patient Perspectives on the Impact of Rare Diseases: Bridging the Commonalities," which was held on April 29, 2019. This public meeting was attended by patients, caregivers, patient advocates, industry representatives, and FDA staff. These attendees came together to share and learn more about how patient perspectives can inform the development of new treatments, and to learn about the commonalities that patients with different rare diseases experience. It was an opportunity to gather information directly from patients and caregivers about how rare diseases impact their lives, and their opinions about current and future treatments. We commend the FDA for sponsoring this meeting to bring together this group of patients and caregivers, and for the support by a panel of FDA staff involved with rare diseases and patient advocacy.

It is widely recognized that patients are the experts on their diseases and have invaluable contributions to make throughout the development of therapies to treat their diseases. This meeting was attended by patients and families, both present as well as

attending remotely, affected by a wide variety of rare diseases. The meeting explored patients' reports of unique aspects of rare diseases as well as commonalities that many of these diseases share. This type of direct patient information can help advance medical product development as well as possibly streamline study designs and other aspects of drug development across a variety of rare diseases.

James Valentine and Larry Bauer attended from Hyman, Phelps, & McNamara, P.C. Both James and Larry have prior FDA experience related to the topics of rare diseases and patient engagement. Our firm represents over 24 patient advocacy organizations that have contributed patient experience data through Externally-Led Patient Focused Drug Development (EL-PFDD) meetings, or through other methods. We have participated in the planning and moderation of over 16 of the approximately 26 such meetings held to date (see Table 1). The EL-PFDD meetings are modeled after the 26 FDA-led PFDD meetings that were held at the Agency starting in 2013. Our experience has given us a unique vantage point to hear from hundreds, if not thousands, of rare disease patients with many different rare diseases. We have seen that while each rare disease is unique in many ways, many of them also share commonalities. To better understand and quantify these findings, we recently analyzed the 11 *Voice of the Patient* reports that were available from the meetings we moderated, which were all for orphan conditions. In this comment, we present these findings as well as compare them to the themes that emerged at this recent FDA meeting.

Table 1: Externally-Led PFDD Meetings Held to Date

Disease	Patient Organization	Date
Amyloidosis*^	Amyloidosis Research Consortium	November 15, 2015
Myotonic Dystrophy*^	Myotonic Dystrophy Foundation	September 15, 2016
Acute Porphyrias	American Porphyria Foundation	March 1, 2017
Osteoarthritis	Arthritis Foundation	March 8, 2017
Spinal Muscular Atrophy*^	Cure SMA	April 18, 2017
Friedreich's Ataxia*^	FA Research Alliance	June 2, 2017
Tuberous Sclerosis (& LAM)*^	Tuberous Sclerosis Alliance	June 21, 2017
C3G, a rare kidney disease*^	National Kidney Foundation	August 4, 2017
Lupus*^	LADA, LFA, & LRF	September 25, 2017
Hyperhidrosis	International Hyperhidrosis Society	November 13, 2017
Duchenne Muscular Dystrophy	Parent Project Muscular Dystrophy	March 5, 2018
Hypereosinophilic Syndromes	Am. Partnership for Eosinophilic Disorders	March 23, 2018
Pachyonychia Congenita*^	PC Project	April 6, 2018
Epidermolysis Bullosa*^	debra of America	April 6, 2018
Sleep Apnea	American Sleep Apnea Association	June 8, 2018
Barth Syndrome*^	Barth Syndrome Foundation	July 18, 2018
Juvenile Idiopathic Arthritis	Arthritis Foundation; CARRA	August 2, 2018
Alport Syndrome*	National Kidney Foundation	August 3, 2018
Chemotherapy-induced hearing loss in pediatric cancers*^	Children's Cause for Cancer Advocacy	September 13, 2018
CMT & inherited neuropathies*	Hereditary Neuropathy Foundation	September 28, 2018
Chronic hypophosphatemias*	XLH Network	October 5, 2018
Cystic Fibrosis*^	Cystic Fibrosis Research, Inc.	October 29, 2018
Major Depressive Disorder	Depression and Bipolar Support Alliance	November 16, 2018
Niemann-Pick Type C	Ara Parseghian Medical Research Fund	March 18, 2019
Mitochondrial Diseases*	United Mitochondrial Disease Foundation	March 29, 2019

*Meetings HPM helped plan or moderated

^Meetings with *Voice of the Patient* reports available, which were assessed for purposes of this comment.

Commonalities in the Rare Disease Experience

Some of the themes that emerged at the March 01, 2019 FDA meeting were themes that we had observed at the EL-PFDD meetings. First and foremost, patients and their families are willing to share their experiences to help define and clarify how their lives have been impacted by rare diseases (11/11, 100%). There has been consistent enthusiasm from patients to talk about the impacts of rare diseases and about the symptoms they experience. These meetings had as many as 80 patient participants who physically attended the meeting, with up to hundreds of patients participating remotely on the web. People traveled from all over the country to be part of this process. The participants included patients who had mobility issues and needed assistive devices to attend. Attendees were motivated to attend despite the ubiquitous report that rare diseases require significant planning, come with a significant burden on how the patient feels and functions, and can result in a period of recovery after pushing through those symptoms. Regardless of the specific disease, several of the themes that were reported by almost all attendees were fatigue, pain, mobility impairment, sleep disturbance, and impacts on ability to fully participate in school and work.

Common disease burden #1: Fatigue

A patient with amyloidosis reported, "I am shackled by a disease that leaves me fatigued and unable to do so many of the things that I enjoy."

Fatigue was a prominent symptom reported by meeting participants as well as EL-PFDD participants (11/11, 100%). Fatigue and low energy can be a result of specific disease effects on body systems, psychological impacts like depression and anxiety, burdensome treatment regimes, and muscle issues affecting ambulation.

An artist with DM1 commented: "When I could no longer stand at my easel, I sat in a wheelchair. When I began to slump over, my back and shoulder muscles tired from sitting, we would use a bungee cord to strap me into an upright position."

Patients with a rare kidney disorder called C3G reported fatigue in both those who had well-preserved renal function as well as those who had progressed to dialysis and kidney transplant.

"Even after a full night of sleep, it looked like she [daughter with C3G] hadn't slept for 24 hours."

Common disease burden #2: Sleep disturbance

Related to fatigue was the common theme of sleep disturbance (9/11, 82%). This seemed to vary in range from interrupted sleep to the need for almost constant parental vigilance throughout the night. One parent spoke about their child's symptom of severe itching skin (pruritus), requiring them to frequently monitor their child throughout the night to prevent them from injuring themselves from extreme scratching. Several parents talked about their own exhaustion because of the sleep disturbance they experience taking care of their child.

"Excessive daytime sleepiness results in lack of energy and motivation to accomplish even the simplest household tasks, such as handling mail or doing a load of laundry," said one caregiver of a patient with DM.

"My daughter has a chronic cough. There is a self-consciousness in standing out constantly…but it's also that she doesn't sleep well because she's coughing through the night. She's literally displaced her ribs from coughing so hard, which is excruciatingly painful and impacts respiratory clearance. This has been a hard thing for her, pretty much her whole life."

– Siri, mother to Tess, 23 Years old with CF

Common disease burden #3: Pain

Pain was a symptom reported by many people with rare diseases (10/11, 91%). Although pain was often not the primary symptom of a disorder, it was often present. Pain frequently added to the disease burden and could involve multiple body systems e.g., kidney effects, respiratory deterioration, muscle and joint pain, etc.

A patient with amyloidosis reported, "Each step I take reminds me of the disease because of the pain of neuropathy."

"I've been in constant pain for 18 years. Some days it's less painful but every day I am in pain…I get it all over and I also have fibromyalgia and arthritis so it's basically from my shoulders to my toes. It's the tingling, burning, inflammation pain," said a woman (with lupus) in her 50s.

And a parent of a child with lupus, "There was a point that [my daughter] was not able to walk more than 40 minutes due to joint pain. Literally, she was not able to walk."

In pachyonychia congenita, pain, however, was the primary symptom that people reported.

A man in his fifties with pachyonychia congenita used the analogy of a bank account to describe the careful planning required for daily activities due to limited mobility - how the plantar pain of PC controls his life: "This one (bank account) isn't one filled with money, but instead it's filled with a number of steps that I can physically walk each day before tremendous pain sets in for me. And just like a checking account filled with money, I spend it very wisely, or try my best."

Common disease burden #4: Mobility impairment

Muscle weakness and immobility are common to many rare diseases (10/11, 91%). In SMA, these symptoms are so evident that parents often seek a diagnosis during the first six months of a child's life.

A parent of a child with SMA observed, "She wasn't getting into the crawling position and having enough strength in her legs to hold a standing position like regular, typical babies do at around five, six months."

People with C3G may develop edema and swelling in their feet and ankles which can inhibit their ability to walk. One patient said that there were several instances when her husband had to carry her into the house from her car because her ankles were so swollen that she couldn't bend them to walk.

A patient with C3G compared herself to her identical twin sister who does not have C3G: "Where her endurance increased, mine decreased; when her flexibility increased, mine declined; where she now stands at five feet six inches, I am four inches shorter."

Common disease burden #5: Decreased ability to perform ADLs

A patient with amyloidosis shared, "I required around-the-clock care. Someone had to lift me to a sitting position to eat. I had to be lifted out of the bed to use a bedside commode… Getting to the shower and bather felt like a marathon."

A fifth ubiquitous impact of rare diseases is a decreased ability to participate in school, work, and to perform activities of daily living (ADLs) (11/11, 100%). Fatigue and sleep disturbances contribute to this as well as mobility issues and complex treatment regimes. Disease burden often leads to social isolation for both the patient and their family members. One patient shared,

"When you face a diagnosis with no cure, most of the life you once knew disappears. Family and old friends just can't bear the burden of my disease and they fade away." (Friedreich's Ataxia)

"I didn't attend parties or large events because I couldn't hear what was going on. The music was really loud, so I went upstairs. Even one floor away, it was still too loud for me. I tried to have conversations with people, but I had to spend so much energy focusing on their face trying to figure out what they were saying, that after three conversations, I went and sat in the corner exhausted from having to focus so hard," she said. (Chemotherapy-induced hearing loss)

Other common disease burdens: Multi-systemic, heterogenic expression, and premature death

The *Voice of the Patient* reports identified many commonalities between diseases beyond individual symptoms and burdens. Every group of patients said that their disease affected multiple body systems (11/11, 100%). An example is people with Barth Syndrome having cardiomyopathy, neutropenia, muscle weakness, growth retardation, metabolic consequences, and poor exercise tolerance.

"Everyone with Barth syndrome seems to have essentially the same constellation of issues, though the degree and severity of each varies by patient."

Another finding from all the meetings was that, while patients experienced a plethora of symptoms, there were always one or two symptoms that seemed to cause the most impact to peoples' lives. For example, Friedreich's Ataxia affects multiple systems, but the patients most commonly talked about the debilitating effects of fatigue (both general fatigue and muscle fatigue), and progressive loss of balance and the ability to walk.

Ten of the eleven reports identified within disease genetic variability (10/11, 91%), and all eleven had heterogenic phenotypic presentations (11/11, 100%). For example, Spinal Muscle Atrophy, one of the most prevalent rare diseases affecting children, has four distinct types varying in age of onset and physical effects. Eight out of the eleven diseases caused premature death (8/11, 73%).

"At times in a given individual, renal complications, for example, may be the most medically pressing Tuberous Sclerosis manifestation; at other times, in the same individual, seizures may be the symptom most impacting the way the person feels and functions or, in fact, survives."

Friedreich's Ataxia is multi-systemic, affecting the neurological system – e.g., balance, fine motor skills, sight, and hearing – and also the heart, skeletal muscle, skeleton (scoliosis, pes cavus), and digestive system (diabetes). While neurological features of the disease are fully penetrant, affecting 100% of those diagnosed, other systems are not affected in all patients. Two-thirds of patients develop cardiomyopathy, more than half develop severe scoliosis, and the incidence of diabetes is between 10 and 40%.

"My son has had many of the complications already mentioned in the meeting: meconimum ileus surgery, 28 courses of intravenous antibiotics, multiple PICC lines, broviac, port-a-cath, many line complications, chronic colonization with MRSA, NTM infection, etc."
– Laura, mother to a 22 year-old son with CF

Common treatment goals

Both at the FDA workshop and all the EL-PFDD meetings, patients and caregivers expressed wanting to find therapies that were curative if possible but, if not curative, that would slow disease progression (11/11, 100%). Parents of children having seizures due to Tuberous Sclerosis said that although complete elimination of seizures would be ideal, a more realistic, but still valuable outcome, would be reduction of seizures. Many reported the ideal treatment would address some of the most life-impacting symptoms. People with Pachyonychia Congenita (PC) said an ideal treatment would treat their pain and increase the length of time that they were able to walk and do activities. One parent stated:

"Finding treatments for the foot pain caused by PC will improve my daughter's quality of life and open many doors for her future, as for all PC patients."

All eleven patient groups reported that current therapies do not adequately treat their disease (11/11, 100%). Some talked about the challenges of administering the available treatments (6/11, 55%), and others reported that the available therapy helped with symptoms, but had unpleasant side effects (6/11, 55%). Three of the groups said that the number of pills per day they had to take was excessive and burdensome (3/11, 27%). Several said that the approved treatment for their disease became less effective over time (2/11, 18%).

Unique to each disease was the specific cluster of symptoms associated with the disease. Each EL-PFDD meeting helped identify the predominant symptoms experienced by patients and those that caused the most challenges. This type of information can only

be obtained by asking patients and their caregivers, yet may be critically important when developing products to treat rare diseases. They also identified which symptoms might be treated to some degree by existing therapies as well as what symptoms remain undertreated or not treated at all.

Regarding the desire for future treatments, it was surprising that many of the patient groups did not identify reversing damage as a goal (only 6/11, 55%). Instead, slowing disease progression and improving quality of life were identified as being of primary importance (10/11, 91%). Preserving functioning and prolonging life were also common to most of the patient groups (10/11, 91%). When considering the benefits and risks of new therapies, many of the groups said that they were willing to tolerate some risk but would need serious consideration if the potential risks were serious or life-threatening (8/11, 73%).

Common perspectives on clinical trial participation

Most, but not all, EL-PFDD meetings specifically asked patients to provide their experiences and preferences related to participating in clinical trials (only 10/11, 91%). Several of the groups said they wished that inclusion criteria in clinical trials were broader so not to exclude too many people from the possibility of participating in a trial (3/10, 30%). Two of the groups said that they would consider participating in a trial even if did not benefit them but rather people with their disease in the future (2/10, 20%).

Additional observations on common experiences

One additional observation is that during some PFDD meetings, certain symptoms had such a powerful impact that, perhaps, some other symptoms were only minimally mentioned. For example, a patient with tuberous sclerosis did not specifically report pain as a symptom but stated:

"I went straight to the emergency room at the hospital and had 12 liters of chyle drained from my pleural cavity. It was so bad, I was secreting up to 3 liters of fluid into my chest cavity a day, and my doctors were worried that my body would eventually give up."

In some cases, the pain from the disorder was related to the treatment consequences. A patient with tuberous sclerosis states:

"To this day, I wake up almost every night with intense pain from the scarring I developed from that nephrectomy."

Pain and sleep disturbances were barely mentioned by people with Friedreich's Ataxia but are probably commonly experienced. Patients with C3G reported pain, fatigue, infections, anxiety and depression, but did not specifically report sleep difficulties.

These observations might suggest that a list of the common symptoms we have described above be asked about at future PFDD meetings.

In conclusion, we congratulate FDA on a successful and important meeting. Bringing patients together to help identify commonalities and differences between their various rare diseases was informative and productive. The meeting demonstrated the FDA's continued support of patients with rare diseases and the shared goal of expediting the development of treatments for their care.

We hope to have provided suggestions that will be informative. Should you have any questions or desire clarifying information, please contact me at jvalentine@hpm.com, or at (202) 724-1745.

Sincerely,

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