

The Voice of the Patient

A series of reports from the U.S. Food and Drug Administration's (FDA's)
Patient-Focused Drug Development Initiative

Neurological Manifestations of Inborn Errors of Metabolism

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Center for Drug Evaluation and Research (CDER) and
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Introduction

On June 10, 2014, FDA held a public meeting to hear perspectives from people living with a set of conditions known as inborn errors of metabolism (IEM). The meeting enabled discussion on the impact that neurological manifestations of IEM disorders have on patients' daily lives, as well as discussion of currently available therapies, and patient considerations related to drug development. FDA conducted the meeting as part of the agency's Patient-Focused Drug Development initiative (PFDD), an FDA commitment under the fifth authorization of the Prescription Drug User Fee Act (PDUFA V) to more systematically gather patients' perspectives on their condition and available therapies to treat their condition. As part of this commitment, FDA is holding at least 20 public meetings over the next five years, each focused on a specific disease area. More information on this initiative can be found at <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm326192.htm>.

Overview of inborn errors of metabolism

Inborn errors of metabolism (IEM) describes a group of rare genetic metabolic disorders that result from deficiencies of specific enzymes, which leave the body unable to properly metabolize, break down, or synthesize certain important substances in the body. Metabolic dysfunction can cause progressive and permanent damage by (a) causing accumulation of a substance to toxic levels in the body; (b) depriving the body of essential substances, such as amino acids, needed to support specific functions; or (c) altering other (unknown) metabolic pathways. There are hundreds of known IEM disorders, including phenylketonuria (PKU), lysosomal storage disorders, Wilson disease, and many others. Individually, most IEM disorders are very rare, but collectively, they account for a significant disease burden in our population. Many IEM disorders are fatal in infancy or childhood; others may progress quite slowly, allowing patients to live to adulthood. For some IEM disorders, clinical manifestations may not be apparent until adulthood.

The effects of IEM vary greatly depending on the underlying disorder, and may affect each major organ system in the body. Commonly, however, IEM manifest as a wide spectrum of neurological signs and symptoms including seizures, cognitive or behavioral problems, language delay, sleep problems, weakness, difficulty swallowing, balance problems, bowel or bladder problems, pain, and other symptoms. These neurological impacts present a significant burden to patients and their families. For this Patient-Focused Drug Development meeting, FDA believed that it was important to explore these symptoms further so that they may be better accounted for in drug development for these diseases.

Current therapies are limited for IEM disorders. Enzyme replacement therapies are available for some diseases, and bone marrow transplantation may be an option for some patients. Advances in gene therapies may provide an option for some patients in the future. Other therapies include dietary restrictions, dietary supplementation, or medical foods. Most commonly, patients who have diseases without an approved treatment utilize supportive measures that don't alter the course or treat the underlying cause of the disease.

Meeting overview

This meeting provided FDA the opportunity to hear directly from patients and patient caretakers about their experiences with IEM and its treatments. Approximately 25 IEM patients or patient representatives attended the FDA's Patient Focused Drug Development meeting in-person, and about 25 additional patients or representatives provided input through the live webcast and polling questions. Although

most participants were parents of a child or children with an IEM disorder, a few participants (in-person and on the web) were people living with an IEM disorder who spoke on their own behalf. In-person and web participants represented a number of IEM disorders, including (but not limited to): Batten disease, creatine transporter deficiency (CTD), Gaucher's disease, isovaleric acidemia, Leigh's disease, metachromatic leukodystrophy (MLD), mitochondrial disease, mucopolisaccharidoses [including Hurler/Hurler-Scheie syndrome (MPS I), Hunter syndrome (MPS-II) and Sanfilippo syndrome (MPS-III)], Niemann-Pick disease, phenylketonuria (PKU), vanishing white matter disease, and Zellweger syndrome. Notably, participants appeared to be highly connected through social media and research and support foundations, and were familiar with drug development and regulatory processes.

Meeting discussion focused on two key topics: (1) disease symptoms and daily impacts that matter most to patients and (2) patients' perspectives on current approaches to treating inborn errors of metabolism. The questions for discussion (*Appendix 1*) were published in a [Federal Register notice](#), announced prior to the meeting. For each topic, a panel of patients and patient representatives (*Appendix 2*) shared comments to begin the dialogue. Panel comments were followed by a facilitated discussion inviting comments from other patients and patient representatives in the audience. The discussion was led by an FDA facilitator, and a panel of FDA staff (*Appendix 2*) asked follow-up questions. Participants who joined the meeting via live webcast were able to submit comments throughout the discussion, and their comments are incorporated into this summary. In-person and web participants were periodically invited to respond to polling questions (*Appendix 3*), which provided a sense of the demographic makeup of participants, as well as of how many participants shared a particular perspective on a given topic.

To supplement the input gathered at the meeting, patients and others were encouraged to submit comments on the topic to a [public docket](#),¹ which was open until August 11, 2014. Fifteen comments were submitted, the majority of which were submitted by individual IEM patients or their caregivers. The comments received via the public docket have been incorporated into this summary.

More information, including the archived webcast and meeting transcript, is available on the meeting website: <http://www.fda.gov/Drugs/NewsEvents/ucm387057.htm>.

Report overview and key themes

This report summarizes the input provided by patients and patient representatives at the meeting, and comments submitted via the webcast and to the public docket. It should be noted that since many IEM disorders primarily affect children who often do not survive to adulthood, patient representatives (most often parents) were a key voice at this meeting. While FDA acknowledges that the diseases and symptoms represented in this report do not represent the entirety of those experienced by IEM patients, we believe that the input provided by meeting participants and docket commenters reflects an adequate range across the spectrum of IEM patient experiences. To the extent possible, the terms used in this summary to describe specific experiences and perspectives reflect the words used by the participating patients and families. This report is not meant to be representative in any way of the views and perceptions of any specific group of individuals or entities. There may be symptoms, treatments, or other aspects of these diseases not mentioned in this report.

¹ A *docket* is a repository through which the public can submit electronic and written comments on specific topics to U.S. federal agencies such as FDA. More information can be found at www.regulations.gov.

The input from the meeting and public docket underscores the devastating effect that inborn errors of metabolism have on the lives of patients and their families and the challenges they face in finding therapies that can help them lead manageable lives. Several key themes emerged from their input:

- IEM encompasses a wide spectrum of diseases, varying greatly in their onset, symptoms, severity, and progression. Input from the meeting and accompanying public docket, which referenced over 15 conditions, reflected this wide spectrum. It included the voices of teens and adults who are able to live more or less functional lives with their disorders, as well as voices for children who have lost or who will lose their battle with their disease early in life. Although their experiences vary greatly, participants shared common perspectives on the significant burdens that these disorders impose on the lives of patients and their families.
 - The parents of children with severely degenerative conditions focused on the loss of their children’s ability to communicate, to make sense of the world around them, and to function independently. These participants conveyed the emotional toll – on their children and on themselves— of helplessly watching the progressive worsening of symptoms, and in particular, the loss of abilities the child once had.
 - Participants representing diseases that are comparatively less severe or better managed expressed gratitude for therapies that enable patients to live longer and more functional lives. However, they stressed that their diseases are “not yet solved,” and that patients still struggle with neurological and other effects, particularly given the challenges of complex treatment regimens.
- The significance of cognitive and behavioral effects was shared by most. As one mother explained, “While each day we deal with the obvious hurdles [like the inability to speak], it's really the secondary sensory, behavioral, and cognitive symptoms that seem to most impact [my son’s] daily stresses and struggles.” Participants described the daily challenges with effects such as diminished learning capacity, altered executive functioning and social skills, and for some, the inability to recognize sources of danger posed by the environment or their own behavior. They also conveyed the interconnectedness of these effects, for example, aggressive behavior exacerbated by the loss of the verbal communication, and anxiety stemming from a lack of situational understanding.
- Although the specific treatments vary widely across the spectrum of IEM disorders, participants shared common experiences with complex and burdensome regimens; these involved enzyme replacement therapies (when available), medications addressing specific symptoms (such as hyperactivity), medical foods and strict dietary control, physical and behavioral therapies, and non-drug and assistive technologies. Many participants indicated that their treatments do not address cognitive and behavioral effects. The parents of children with severe degenerative diseases stressed that absent a cure, what they desire most are treatments that can slow disease progression and maximize quality-of-life for as long as possible. Secondly, participants across the spectrum expressed a desire for therapies that are more targeted or less burdensome.
- Participants expressed urgency for more and faster advancements in drug development, including clinical trials for experimental therapies. The parents of children with severe degenerative diseases reiterated that their children are dying, and as parents, they want their children to have the opportunity to participate in clinical trials. They conveyed a willingness to

consider and accept a high degree of risk and uncertainty for the possibility of benefit from those therapies. More generally, participants stressed the importance of: reducing barriers to clinical trial participation; streamlining the informed consent process (with an understanding of the consent issues unique to this population); enabling expanded access to experimental treatments; and facilitating broader access to medical foods and other treatments.

Patient and caregiver input from this meeting and accompanying public docket strengthens our understanding of the therapeutic context of IEM. FDA staff will carefully consider this input when advising sponsors on their drug development programs, providing oversight on investigational new drugs, and assessing products under review for marketing approval.² This input may have broader applicability for drug development for IEM, for example, by identifying potential opportunities to develop new clinical outcome assessments, or by informing development of clinical trial protocols and informed consent documents.

Discussion Topic 1: Disease Symptoms and Daily Impacts That Matter Most to Patients

The first topic of discussion at the meeting focused on patients' experiences with their IEM symptoms. In particular, FDA asked participants to discuss the neurologically-manifested symptoms, and the impacts those symptoms have on the lives of patients and their families. To start the dialogue, five panelists, all parents of a child or children with various IEM disorders, shared their experiences. These participants described the daily challenges their children have faced with their respective conditions, and shared the significant fears, frustrations, and stresses they experience because of their child's or children's condition. Their testimonies provided a rich context for dialogue over the course of the meeting, and nearly all patients and patient representatives in the audience indicated (by a show of hands) that their or their loved one's experiences were reflected in the panelists' comments.

The discussion of disease symptoms reflected the wide variability in the IEM disorders and their manifestations. For example, the discussion touched upon the life of a toddler (Gaucher's disease) whose symptoms appeared shortly after birth and who passed away at age three; two siblings (Batten disease), ages eight and 10 who "started life as happy normal kids" but have gradually lost all motor, sight, and verbal ability; a 16-year-old boy (isovaleric acidemia) who at 3 ½ years of age suffered, without warning, a severe brain injury "crisis" resulting in severe disabilities; and a young man (PKU) who manages his disease while preparing to graduate college. Across this spectrum of experiences, a range of symptoms and impacts were discussed. In general, these symptoms appeared to fall into two broad categories: those that relate to behavioral and cognitive issues, and those that relate more to physical and motor disabilities. (Note that while FDA focused discussion on neurologically-manifested symptoms to narrow the meeting scope, this report includes all symptoms and impacts described at the meeting, without giving priority to any one symptom or impact.)

² Previous *Voice of the Patient* reports developed to summarize Patient-Focused Drug Development meetings have included an appendix with a sample benefit-risk framework developed from meeting input, demonstrating how meeting input may inform completion of benefit-risk assessment frameworks for specific products under review. Because the Inborn Errors of Metabolism meeting covered multiple conditions, this report does not include such a sample framework.

Perspectives on Cognitive and Behavioral Symptoms

Impaired Cognition/Executive Function

Most in-person and web participants and docket commenters commented on the cognitive effects of IEM. In response to a polling question (Appendix 3, Q5), nearly two-thirds of responding participants identified cognitive impairment as one of the symptoms with the greatest impact on daily life. Throughout the discussion, many participants indicated that these effects are among the most impactful on the daily life and well-being of IEM patients and their caretakers. Participants also commented on the progressive, degenerative, often-irreversible nature of the cognitive effects of various IEM disorders. The following examples illustrate the experiences shared by meeting participants and docket commenters in regards to impaired cognition. (The specific disease discussed by the participant or docket-commenter is indicated in parentheses.)

- One woman described her sister's (PKU) impaired executive function at a time when her blood phenylalanine levels were not under control, saying, "I would take her shopping ... and it [took her] five minutes to pick which bananas she wanted to take home." She noted that her sister's decision-making abilities improved significantly once her phenylalanine levels were under control.
- A mother commented that her son's (CTD) cognitive impairments leave him without any recognition of danger, with no hesitation to "run into a busy street, walk out the front door, jump on my dining table, or walk right into a swimming pool."
- A mother described how her son (Hunter syndrome) rapidly lost 18 IQ points in only eight months as his disease progressed. A father of three children (Hurler-Scheie syndrome) also described their notable loss of IQ over time.
- One participant (PKU) noted the problems with controlling his temper and the lack of focus he experiences in school when his blood phenylalanine (Phe) levels are even slightly elevated. Other participants representing PKU shared similar experiences.

Behavioral Effects

Behavioral effects were also addressed during the panel comments and the large-group discussion. About half of responding participants (Appendix 3, Q5) identified behavioral problems as one of the symptoms with the greatest impact on daily life. Participants described their or their children's difficulty in social situations, inappropriate public behavior, aggression, hyperactivity, anxiety, phobias, and even issues with self-harm. Many parents also said that the behavioral issues are often exacerbated by their child's significant developmental, communication, or motor disabilities, including the "limited ability to understand the situation [and] the environment" (Leigh's disease), "going weeks without sleeping" (Sanfilippo syndrome), "inability to manipulate toys" (CTD), "frustration [knowing] that he used to be able to do something and that he couldn't anymore" (Sanfilippo syndrome), and frustration with the inability to speak (Sanfilippo syndrome). One parent (mitochondrial disease), however, cautioned against attributing behavioral effects largely to situational factors or as a response to other symptoms: "In reality, [the behavioral issues are] caused by ... the defect in the pathway... and if we could approach that, maybe we could improve the behavior."

Inability to Vocalize or Speak

A subset of participants, including those representing Sanfilippo syndrome, CTD, Batten disease, and Hunter syndrome, commented on the significance of their loved one's difficulty with speaking. This was also described as a progressively worsening symptom, eventually rendering many patients completely unable to communicate verbally. One mother noted how her son's (Hunter syndrome) speech began to lessen from complex sentences to "three- to four-word sentences... and he began to stutter uncontrollably." A father described his children's (Batten disease) waning vocal ability as "stutter[ing] a sentence that they were never able to complete." Another parent expressed his grief as he watched his son (Sanfilippo syndrome) "going from nearly a normal child to not being able to speak in about six months."

Parents expressed the far-reaching burden stemming from their loved one's lack of verbal communication. One father described how his son's (Sanfilippo syndrome) inability to speak makes it difficult to know how "to help [him] on a daily basis." Another parent stated the particular challenge in the non-verbal patient being unable to communicate their pain. A few participants commented on the impact on behavior; as one mother described, "without speech" her son (CTD) resorts to "screaming, biting, or pulling [his siblings'] hair" as an outlet for his vexation. A father (Sanfilippo syndrome) further explained that "the language gave structure to [my daughter's] world [and] that went away. When there's no language, there's no rules, there's no reason for us behaving one way or another."

Psychiatric Effects

Some meeting participants identified psychiatric effects of IEM as a particularly troubling group of symptoms. For example, a father commented that his daughter (Hurler-Scheie syndrome) had developed mania, depression, and psychosis leading to delusions and hallucinations, hearing voices, and going weeks without sleep. He described the significant impact these symptoms have on his daughter's quality of life, adding that "at 22 years of age, [she] cannot be left alone." Another participant explained that her grandson (MLD) has "hear[d] voices telling him to hurt other people." A few participants commented on obsessive and compulsive behavior, including pica ("constantly chewing things"), and licking strangers.

Perspectives on Physical and Motor Symptoms and Disabilities

Seizures

Seizures or epilepsy were mentioned by many meeting participants and docket commenters, representing a number of IEM disorders including (but not limited to) Hunter syndrome, PKU, Zellweger syndrome, and CTD. About one-fifth of responding participants (Appendix 3, Q5) identified them as one of the symptoms with the greatest impact on daily life. These participants stressed that seizures, which often progressively worsen, are particularly debilitating and cause a significant amount of stress for both patients and their caretakers. As one parent (Batten disease) explained "[seizures] exhaust their small bodies, add damage to their brains, and leave us as parents feeling helpless and terrified." This participant further stated that some of the other symptoms his children experience may actually be a result of the seizures or of the treatment required to manage them.

Bowel and Bladder Issues

Approximately one-third of meeting participants identified bowel or bladder issues as one of the symptoms with the greatest impact on daily life. These participants noted the particular challenges associated with the gradual loss of bowel and/or bladder control. For example, one parent described how her two children, ages eight and 10 (Batten disease) must be diapered due to their loss of bowel and bladder control. Another mother remarked that towards the end of her daughter's life (Gaucher's disease), she had completely lost the ability to urinate on her own.

Mobility Issues

A few participants focused on the inability of their children to mobilize or exhibit coordinated motor functioning. This again was described as a gradual impact, becoming progressively worse as the disease advances. For one parent, his children's (Batten disease) ataxia led him "to restrict the last remaining freedoms [they] had," and he noted their apparent frustration as they continued to lose motor function, eventually becoming immobile and wheelchair-bound. Another parent detailed all three of his children's (Hurler-Scheie syndrome) inability to mobilize, whether through walking or crawling.

Sensory Impairment/Processing Issues

Nearly one-third of participants identified sensory impairment as one of the most significant symptoms of their IEM disorder. The gradual loss of vision was mentioned as a particularly troubling symptom of various IEM disorders, and one father noted the terror his two children (Batten disease) experienced as their sight gradually disappeared and their "world went dark." A docket commenter also noted that it is particularly difficult to determine the level of her children's (Zellweger syndrome) cognitive impairment, due to their deaf-blindness.

Sensory processing issues, especially the intolerance for clothing and certain foods, were also mentioned. One patient's mother described the significance of her son's (CTD) intolerance for clothing, which frequently results in him removing his clothing in public. A web commenter (mitochondrial disease) noted the difficulties she has in regulating her body temperature, and that she's experienced "feet so cold that they hurt."

Difficulty or Inability to Swallow

Some participants described the progressive inability to swallow, which eventually leaves some IEM patients reliant on feeding tubes or suction devices for saliva removal. As one mother described, her children (Batten disease) "require round the clock suctioning to prevent [them] from drowning on their own saliva secretions," and that she had made the decision to take away oral foods because "the choking hazard is simply too high." The parent of a deceased child (Gaucher's disease) believed that neurological symptoms, such as laryngeal spasms, were one of the sources of his child's swallowing difficulties.

Sleep Issues

A few participants commented on the significance of sleep issues. One parent noted that her son (PKU) experiences troubling nightmares, night tremors, and even sleep walking. Two participants noted how their children (Sanfilippo syndrome, MELAS-like syndrome/Type B pyruvate carboxylase) have difficulty sleeping, occasionally being unable to sleep for long periods of time. Another parent described her daughter's (Gaucher's disease) sleep apnea and breath-holding, which led to the need for a ventilator.

Pain

Although it did not involve much discussion during the meeting, nearly half of responding in-person participants identified nerve or abdominal pain as one of the symptoms with the greatest impact on daily life. In addition, a web participant (Hunter syndrome) described the debilitating migraines he experiences for five to six days each month, which prevent him from completing basic activities like chores, or socializing with friends. A mother described how her daughter's (Gaucher's disease) increased muscle tone caused pain to the point that she was eventually unable to sit up, crawl, or roll over.

IEM Symptoms' Impacts on Daily Life

Notably, because a majority of the individuals affected by IEM disorders are children, many of the impacts of the disease are felt by patients' families and caregivers. Additionally, because many IEM patients experience cognitive difficulties, and sometimes even early death, the voice of the patients' parents was central to this meeting. Therefore, there was a notable focus on the burden faced by caregivers of IEM patients during this meeting, whether in-person, on the web, or in docket comments.

Impact on IEM Patients

Many participants focused in particular on the impossibility of their IEM-afflicted children ever living a "normal" or independent life. They stressed the all-encompassing nature of the disease, which prohibits or complicates many day-to-day functions for IEM patients. One father described how his children (Hurler-Scheie syndrome) "understand that they have cognitive limitations that make it difficult for them to consider normal activities, such as driving a car, going to college, having close friends, getting a normal job, or ever living alone." Another parent provided a picture of the burden on both caregiver and IEM patient when she described how her son (Hunter syndrome) had to be "strapped in a pediatric wheelchair with a six-point harness." One participant (PKU) described the stigma he faced as a child when he would bring "fake processed foods" to school for lunch as part of his restrictive diet, and described the difficulties he now faces as a young adult in maintaining a "normal" life with the burdens imposed by his strict diet and multi-pill regimen.

Participants also stressed that for patients on the most extreme end of the severity spectrum, the gradual sensory impairment and loss of motor and vocal abilities is particularly terrifying. A few parents shared that their children were cognizant of their physical decline and expressed their pain and dismay either verbally or through their behaviors. For example, one father mentioned how his daughter (Batten disease) watched as her older brother (Batten disease) lost his abilities, and would "often cry to us [asking] if she would become like [him]" as she too began experiencing the same symptoms.

Impact on Caregivers and Families of IEM Patients

Parents and caregivers also discussed the difficulties they face in maintaining the sense of a "normal life" for themselves and their families, especially due to their child's IEM-related behavioral issues. One parent described her child (CTD) as a "Tasmanian Devil... because in a three-minute timeframe, he's woken up, he's pulled his diaper and clothes off, he's spilled a drink off the counter, he's pulled a bag of cereal down and it's all over the floor, and he's dancing on my dining table... and there are two other children in the house who also need care." Other participants echoed the stresses placed on the family because of their child's IEM-related behavioral issues, particularly behavior exhibited in public. One docket commenter, the older sister of three brothers with Hunter syndrome, described how she and her

older sisters had “no childhood or teen years... because it was their “[duty] to take care of the excessively hyper-active [brothers] and [their] episodes of diarrhea constantly.”

Beyond the daily stresses, participants across the spectrum of disease described their pain and worry about their children’s well-being, and for those facing the severely degenerative diseases, the suffering their families face as they watch their child become progressively worse. As one parent (Batten disease) explained, “making the decision to take [away] oral foods [that your child] once loved, because the choking hazard is simply too high, is something no parent should ever have to do.” A mother commented that while she feels blessed that her sons’ condition (PKU) is manageable, she worries how they “will manage PKU on their own as they grow into young men.”

Defining a “Good Day”

FDA asked participants to share their perspectives as to what constitutes a “good day” in their experience with their IEM disorder. Participants, primarily parents, were able to pinpoint distinct and noticeable differences between such days and “bad days.” They provided a range of attributes of their children’s “good days,” including being able to act more independently, keeping their behavior more in control, sleeping at night, and keeping spirits high. For a few, a good day was simply being able to keep their child safe. The following examples illustrate their perspectives:

- One mother (Vanishing White Matter disease) said that a “good day” is when her daughter is “able to participate with me, help me transfer her [to and from her wheelchair]... and [when] she can eat without food getting stuck.”
- A father (Sanfilippo syndrome) shared that a “good day” was when “I had communication, eye contact, [and my daughter would] sit and stare at me for long periods of time and just interact personally. And that was powerful.”
- A father (Batten disease) indicated that number one is a day without seizures (given the damage that is sustained) and that in addition, a “good day” is “getting a smile... being able to regulate body temperature... [and] having bowel and bladder movements.”
- A mother shared her sons’ (PKU) lack of anxiety and notably increased ability to concentrate and focus at school, on “good days” when their blood phenylalanine levels are under control.
- A mother (CTD) noted that the “good days” with her son are the ones where he is “a little bit more cooperative and a little bit more even-keeled.”

Discussion Topic 2: Patient Perspective on Treating Inborn Errors of Metabolism

The second main topic of discussion focused on patients’ experiences with therapies used to treat their or their loved ones’ condition. Five panelists, including four parents (Hunter syndrome, MLD, and Sanfilippo syndrome), and one person living with PKU provided comments to start the dialogue. Panelists shared their and their children’s experiences with a variety of treatment regimens, including prescription medications and lifestyle changes. In the large-group facilitated discussion that followed, nearly all participants in the audience indicated, by a show of hands, that their experiences were reflected in the panelists’ comments. Most participants indicated, in response to a polling question, that

they rely on multiple therapies to help manage or treat their IEM disorder, although a few in-person participants reported using no therapies – prescription or otherwise.

The following is a summary of the treatment experiences described through comments made at the meeting, on the webcast, or submitted to the public docket. A few key themes emerged during the second topic portion of the meeting, most notably: 1) The current lack of effective treatments for these disorders; and 2) Many participants’ willingness to try any therapy that may slow disease progression, or that may improve how the patient feels or functions. During this portion of the meeting, participants also discussed considerations for clinical trials and drug development more broadly, a summary of which concludes this section.

Perspectives on Medical Treatments for IEM

Enzyme Replacement Therapy (ERT)

Approximately a quarter of responding participants (Appendix 3, Q6) identified enzyme replacement therapies (ERT) as part of their treatment regimen. These participants expressed gratitude for the impact of these treatments to help their loved ones lead “longer and healthier lives.” One parent noted that with ERT, her son (Hunter syndrome) experienced fewer falls, more energy, better range of motion, improved breathing, increased speaking and “he was happier, because I believe he was in less pain.” She noted, however, that his learning abilities and aggressive and uncontrollable behaviors continued to worsen. Other parents shared similar experiences. A docket commenter also praised the positive effects that ERT had on her daughter’s (Morquio syndrome) quality of life, but lamented that it was not a cure, and would have no effect on her daughter’s lifespan.

A few participants commented on the downsides of ERT treatment, including the time required at the hospital and the need to access veins for infusions. A mother (Hunter syndrome) commented on the burden of the ERT infusion process, but remarked that “I’ll take that if it means it works.” She appreciated being trained to give the infusions at home, rather than being required to visit the hospital for treatment administration. This participant further commented on the importance of addressing issues with immune response.

Other Prescription Medications Approved for the Treatment of IEM Disorders

One patient (PKU) commented that Kuvan (sapropterin) had changed his life “180 degrees” by allowing him to eat less restrictively, but noted the burden of having to take many pills each day. One web commenter stated that her daughter (Gaucher’s disease) had been given miglustat, approved for the treatment of Gaucher’s disease, but the side effects were too significant to allow her daughter to get up to the most effective dosage, and they did not see any neurological benefit from the drug.

Bone Marrow Transplant

A few participants commented on their experience with bone marrow or organ transplantation. One parent described her daughter’s (Hurler-Scheie syndrome) substantial cognitive and motor improvements following a transplant and intense therapy. Another parent, however, shared that his child (MLD) had received a bone marrow transplant at age 10, and had post-transplant rejection complications and passed away.

Other Prescription or Experimental Therapies

About two-thirds of responding participants reported using other prescription medicines, such as anticonvulsants or psychiatric medications, to help manage specific symptoms. For example, one parent commented that his child (MLD) was prescribed Risperdal (risperidone) medication to control aggression, and amitriptyline to help the child sleep. He said both were effective, but had the downside of making the child lethargic the next day. A web commenter discussed using the drug pamidronate for analgesia in managing his daughter's condition (mucopolidosis).

Several participants also mentioned the use of experimental therapies. For example, one participant described her daughter's and son's (MLD) improvements from an experimental gene therapy. A docket commenter described the positive effects that the experimental drug DHA-ethyl ester (DHA-EE) had on her son (Zellweger syndrome) while enrolled in a clinical trial in Barcelona, Spain. More detail on participants' experiences with clinical trials is discussed further in another section of this report.

Perspectives on Diet-Related Treatments for IEM

Dietary Control

Strict dietary control was identified as an essential element of treatment by many participants. Participants representing PKU in particular noted the importance of controlling symptoms by regulating dietary factors that affect the level of phenylalanine (Phe) in the blood, which as one parent explained, requires "a daily formula intake that ...involves weighing the foods ... [and] very meticulous recording of the intake." A web commenter discussed the "low-sodium, anti-inflammatory diet regimen" that helps with his daughter's (mucopolidosis) joint pain "about 25%." Another parent noted that the diet his daughter (MELAS-like syndrome/Type B pyruvate carboxylase) must observe requires his family to "spend more than the average family on food and antioxidants." Other participants noted the particular burden that careful diet management places on their lives.

Medical foods

Medical foods were also discussed as central to treatment for some IEM patients, particularly those patients diagnosed with PKU. An adult patient (PKU) noted the significant, positive impact that medical food has made in the management of her condition, stating: "Medical food is the treatment that I depend upon to this day for health and survival, to perform academically, socially, and professionally, one that spared me a lifetime of institutional care and saved my children's lives."

Nutritional Supplements

Nutritional supplements were also mentioned by a few meeting participants as a part of their IEM treatment regimen, albeit with mixed results. One parent mentioned that he and his family, with "nothing to lose," tried giving their child (Sanfilippo syndrome) the nutritional supplement Genistein (phytoestrogen) but found that the product seemed to have no effect on his child. Another parent noted that her child (MELAS-like syndrome/Type B pyruvate carboxylase) had been given a "mitochondrial cocktail," or a combination of vitamins and supplements, but stated that the treatment did not appear to have beneficial effects.

Perspectives on Other Supportive Care or Assistive Technologies for IEM

Physical Therapy, Occupational Therapy, Behavioral Therapy, Speech Therapy

Physical therapy, occupational therapy, and speech therapy were noted by well over half of meeting participants as a part of treatment for IEM disorders. One mother discussed her daughter's (MELAS-like syndrome/Type B pyruvate carboxylase) regimen of speech, physical, and occupational therapy, as well as "floortime," which she described as a "play therapy to keep her emotionally regulated, to take her to higher levels of thinking and understanding the world around her." She noted that the effects of floortime were especially positive for her daughter. Another parent stated that his children (Batten disease) had both been involved in speech therapy, but lamented that the "countless hours [of it] perhaps only extended their abilities for a few months."

Non-Drug and Assistive Therapies

Many participants commented on the need for non-drug therapies to manage their disorder, including: dialysis, splinting, suction devices for saliva removal, and gastrointestinal tubes. One parent noted the difficult decision to have GI tubes placed in his children (Batten disease) "because the choking hazard is simply too high," and because although he and his wife "would spend hours carefully feeding the children... [they] were losing too much weight." In addition, nearly two-thirds of meeting participants identified the use of some form of assistive technology, ranging from wheelchairs to readers.

Perspectives on an Ideal Therapy

Participants were asked to identify specific attributes they would look for in an ideal treatment for their IEM condition. They provided a range of perspectives summarized below.

- Many participants expressed a desire for treatments that can better address the underlying cause of their disease and slow disease progression, rather than simply addressing symptoms.
- Absent a cure or significant slowing of progression, participants commented on their desire for treatments that can enhance daily quality of life for their child and their family. As one father (Sanfilippo syndrome) explained: "I'm not expecting [my son] to get a medical degree someday. I just want him to live a manageable life."
- One participant (PKU) expressed that an ideal treatment would better target specific genetic characteristics of an individual. She also expressed her concern that current ERTs in development are focused on improving the phenylalanine levels of those who are not well-controlled, but do not seem to address the question of how to "transition adults with PKU who are in stable metabolic control to an enzyme."
- Some parents commented on lessening the burden of treatment, particularly those that require infusion or intrathecal administration. As one parent (Hurler-Scheie syndrome) explained, "taking a pill would obviously be preferred for all the kids on ERT."

Perspectives on Clinical Trials for IEM Drug Development

FDA was particularly interested in hearing patients' and families' perspectives on participating in clinical trials for potential new treatments. Participants' comments on participating in clinical trials and on communicating about clinical trials are summarized below.

Considerations on clinical trial participation

In response to a polling question (Appendix 3, Q7) almost half of participants (or their loved one's) had participated in some type of clinical trial studying experimental treatments for IEM, and several others indicated that they would have liked to have been in a clinical trial but could not for some reason. In response to a follow-up question, all responding participants indicated that they are generally willing to consider participating in a clinical trial if given the opportunity. Participants shared rich insight into the factors they have considered (or would consider) in their decision. The following examples illustrate the perspectives shared.

- One mother (MLD) described initially considering a bone marrow transplant, but how she then discovered a gene therapy clinical trial in Italy. She indicated that the expected benefits of participating in the clinical trial outweighed the risks of the transplant, which had a high mortality rate in this population. The mother relocated to Italy with her two children for four months, and the family had to pay for the drug on their own.
- One parent described her decision to enroll her son (Hunter syndrome) in a clinical trial. She noted the importance of the new drug's potential, and in particular, considering whether it might slow or halt the disease. According to her, "Improvement was not even contemplated. Life is most important and we'd take any shot at it... To do nothing, to us, equaled death." Route of drug administration and risk considerations were lower factors in her decision, "because we know otherwise he would die a slow, difficult, and painful death."
- One parent (MLD) touched on the importance of quality of life considerations, stating that "[it's] not just [about] longevity." He also noted that "when the outcome is death, the risk-reward benefit tables turn quite a bit. And so we're anxious for safe experimental therapies... But if the worst thing that happens in a therapy is nothing, that's okay."
- Another parent (Sanfilippo syndrome) touched upon quality versus quantity of life considerations: "I know that this is a shocking thing for most people to hear ... my son may live 10 more years if we don't treat him, but his quality of life is rapidly decreasing. And I think if I tried something today with a reasonable belief ... that it might help him and he died, I would know that I'd died trying and that would be something that I could live with."
- A few parents stressed the importance of getting into a clinical trial as soon as possible given the degenerative nature of the disease.
- One parent (MELAS-like syndrome/Type B pyruvate carboxylase) described the challenges in managing her daughter's metabolic requirements and indicated that she would need to consider the impact of the treatment on that management and possible unintended damage. She would want to know "how long the experiment has existed, how many patients have been involved in the research, and the key outcomes and statistics."

- A few participants commented on their or their child’s perspective as a patient. For example, one parent described how her eight-year-old son (PKU) expressed his desire to participate in a clinical trial even after he was shown the number of shots required and the thickness of the needle.

Perspectives on risk and uncertainty in IEM drug development

Throughout the meeting, participants across the spectrum of diseases expressed urgency for more and faster advancements in drug development, including clinical trials for experimental therapies. Several participants expressed frustration that certain drug trials have not been conducted in the U.S. even though they have been conducted in Europe.

An important consideration in drug development is how much evidence of safety and efficacy is necessary before an experimental treatment is studied in humans. FDA was particularly interested in hearing participants’ perspectives on these issues with respect to drug development for IEM. To help focus discussion, FDA presented at the meeting a hypothetical scenario³ of a Phase I “first-in-human study” for an experimental ERT that will involve approximately 10 patients. For this trial, there is less animal data available than is typical for a first-in-human study, and the benefits and risks of this treatment are highly uncertain. Participants’ responses to this scenario generally aligned with their perspectives shared throughout the meeting discussion, in particular for the parents of children with severely degenerative diseases. A summary of their comments is provided below.

- Several participants reiterated their willingness to consider greater risk and uncertainty of a clinical trial for their child given the extreme severity of their respective diseases and the current lack of effective treatments for many IEM disorders. As one parent (Sanfilippo syndrome) explained “I think we’re all willing to take more risk. We have to. My son’s going to live three more years... I can’t be in a riskier situation [than that].” Another parent (Sanfilippo syndrome) commented that he would consider whether “reasonable treatment is already available for the disease... and would accept more risk if there’s nothing.” He also described how he would consider the disease state, saying that “if it was very early and [he was] young, and there was hope that I could wait and see some data, then maybe I would sit on the sideline... [but] if the window is very short relative to the time of the trial, I would put him in, no doubt about it.”
- A few participants commented specifically on the requirements for animal safety data and expressed their concern that the safety evaluation requirements for these rare, serious diseases are too stringent. One participant (Hurler-Scheie syndrome) stressed that he was not advocating for the chance to use treatments not yet tested in animals. However, he intimated that IEM treatments needn’t be subject to the same “rigorous thresholds” for safety as treatments for other conditions. Another participant echoed this sentiment, stating that “there does need to be safety data, but [what] can we learn from what we’ve already been doing with [ERTs]?”
- One participant (Batten disease) commented that “[w]e may not expect to be on these treatments for life because in a lot of these conditions, we know that there are second generation treatments coming along.”

³ For the full scenario text, see slide 52 in the meeting presentation, available at <http://www.fda.gov/downloads/Drugs/NewsEvents/UCM401027.pdf>

Considerations on informed consent for IEM clinical trials

Participants were also asked to comment on important considerations regarding informed consent procedures for IEM patients, particularly when the patients are children or have disabilities that hinder their ability to provide informed consent. The following examples illustrate the perspectives shared.

- One parent (MLD) described the difficulties faced by minor and/or cognitively-impaired patients, “with over 50% of the MLD population being three or four years-old by the time [you] are considering something.” In these cases, and in cases of cognitive impairment, he reiterated the importance of allowing caregivers to be actively involved in consent decisions.
- Another parent (MELAS-like syndrome/Type B pyruvate carboxylase) cautioned that because of their desperation, “parents may make an emotional decision not realizing some of the side-effects and risks,” and said that parents need to be given full information. She raised the possibility of mandatory education and a brief waiting period for parents before enrolling their child in a clinical trial.
- However, another parent (Sanfilippo syndrome) cautioned against “just releasing tons of data to patients.” He asserted that since “run-of-the-mill” parents are likely unable to interpret complicated or obscure clinical data, they often simply trust what their doctors tell them. Therefore, he recommended that the information be “boiled down by the sponsor and then the doctor who’s running the trial... [in]to simple language that parents can understand.”
- One participant (Hurler-Scheie syndrome) stressed the importance of “involving the child in the process at the level that they are able to understand.” Another participant (PKU) commented on the value in demonstrating to the child what is involved in the procedures.

Other considerations on drug development

Although the focus of the discussion was on clinical trials, participants raised a number of other considerations on drug development and healthcare for IEM disorders, including the following.

- A parent (Hunter syndrome) commented that “there should be an expectation of compassionate access past the initial safety trial [because] any given trial or drug may be the only shot they have.” However, another participant (MLD) commented that even if FDA does allow compassionate use, in his experience, industry does not advocate for such use because the risks to their drug development program are too high.
- Several participants commented on a need to collect more data through patient-reported outcomes. A few, however, noted the challenge of measuring cognitive and behavioral effects. As one participant (PKU) explained, “as a parent, I don’t even know how to measure [these effects].” Another participant (CTD) commented that it can be difficult to determine if an action such as throwing a cup is “a behavioral thing? A habitual thing? A communication issue?... [or] all of the above.”
- A few participants expressed their desire for becoming a more integral part of the drug development process. One parent (MLD) explained, “We’re very interested as advocacy groups in being on advisory panels, but in many cases, we [cannot meet the] requirements for conflict-

of-interest... We've seen hundreds of families and literally dozens of researchers... [W]e're the experts, and we can't participate.”

- A few participants commented on the challenges with cost and access to therapy, including medical foods and supplements. A few participants also commented on the challenges receiving adequate diagnosis and healthcare for these rare diseases within the healthcare system.

Conclusion

This meeting was the tenth of the FDA’s Patient-Focused Drug Development meetings. It enabled FDA and others to obtain patients’ and families’ points of view, in a systematic way, on the impact that the range of inborn errors of metabolism has on the daily lives of patients and their families, specific neurological symptoms that matter most, available treatment options, and considerations on clinical trial participation. We recognize that patients and their families are experts on what it is like to live with their condition, and as such, they have a unique ability to contribute to our understanding of the broader context of the disease. This understanding is important to our role, and that of others, in the development and evaluation of safe and effective treatments for these serious diseases. In the words of one meeting participant (father of two daughters with MLD) *“We need to have this kind of open exchange consistently... even if it's uncomfortable, because that's where all of this insight and perspective comes from.”*

It is clear that inborn errors of metabolism are a group of debilitating diseases that can have a devastating impact on patients and their families. We are grateful to patients, parents and others who courageously shared their experiences and perspectives. We also admire the strength of the participants, who demonstrated their resolve in the face of adversity presented by their or their loved one’s condition.

Appendix 1: Meeting Agenda and Discussion Questions



Inborn Errors of Metabolism Public Meeting on Patient-Focused Drug Development



June 10, 2014

8:00 – 9:00 am	Registration
9:00 – 9:10 am	Welcome and Opening Remarks Sara Eggers, PhD <i>Office of Strategic Programs (OSP), Center for Drug Evaluation and Research (CDER), FDA</i> Donna Griebel, MD <i>Director, Division of Gastroenterology and Inborn Error Products (DGIEP), CDER, FDA</i>
9:10 – 9:30 am	Background and Context Theresa Mullin, PhD <i>Director, OSP, CDER, FDA</i> Teresa Buracchio, MD <i>Medical Officer, DGIEP, CDER, FDA</i> Sara Eggers, PhD <i>OSP, CDER, FDA</i>
9:30 – 10:00 am	Panel #1 Comments on Topic 1 Topic 1: Neurological manifestations of inborn errors of metabolism that matter most to patients. A panel of patients and patient representatives will provide comments to start the discussion.
10:00 – 10:45 am	Large-Group Facilitated Discussion on Topic 1 Patients and patient representatives in the audience are invited to add to the dialogue.
10:45 – 11:00 am	Break
11:00 – 11:30 am	Panel #2 Comments on Topic 2 Topic 2: Approaches to treating the neurological manifestations of inborn errors of metabolism and perspectives on informed consent for clinical trials.
11:30 am – 12:15 pm	Large-Group Facilitated Discussion on Topic 2
12:15 – 12:45 pm	Open Public Comment
12:45 – 1:00 pm	Closing Remarks Teresa Buracchio, MD <i>CDER, FDA</i>

Discussion Questions

Topic 1: Disease Signs, Symptoms, and Daily Impacts That Matter Most to Patients

1. Of all the signs or symptoms that you/your child experiences because of the condition, which 1-3 neurologic/neuropsychological signs and/or symptoms have the most significant impact on your/your child's life? (Examples may include seizures, decreased muscle tone, sensory issues, etc.)
2. Are there specific activities that are important to you/your child but that you/your child cannot do because of these neurologic/neuropsychological signs or symptoms? (Examples of activities may include sleeping through the night, daily hygiene, going up the stairs, etc.)
3. How have your/your child's neurologic/neuropsychological signs or symptoms changed over time?

Topic 2: Patient Perspectives on Current Approaches to Treating Neurologic Manifestations of Inborn Errors of Metabolism and Informed Consent for Clinical Trials

1. What are you/your child currently doing to help treat the condition or its signs/symptoms? (Examples may include prescription medicines, herbal therapies, acupuncture, over-the-counter products, and other therapies including nondrug therapies such as diet modification.)
 - a. How well does this current treatment regimen treat the neurological symptoms of your/your child's disease? For example, how well do the treatments improve your/your child's ability to do specific activities?
2. Assuming there is no complete cure for your/your child's condition, what specific attributes would you look for in an ideal treatment for the condition?
3. In the informed consent process, what are important considerations to take into account in cases when the potential participant is a child? For example, how should the informed consent clearly communicate to the patient the potential benefits and risks of a study?

Docket Information

We encourage you to submit your written comments to the docket by August 11, 2014: <http://www.regulations.gov/#!documentDetail;D=FDA-2014-N-0396-0001> or go to www.regulations.gov and search for: **inborn errors of metabolism patient-focused drug development**.

Appendix 2: Patient and FDA Panel Participants

Patient Panel, Topic 1

- Whitnie Strass – Mother of a CTD patient
- Christine Brown – Mother of two PKU patients
- Steve Holland – Father of three Hurler-Scheie syndrome patients
- Melissa Bellini – Mother of a Gaucher’s disease patient
- Tracy VanHoutan – Father of two Batten disease patients

Patient Panel, Topic 2

- Melissa Hogan – mother of a Hunter syndrome patient
- Dean Suhr – father of two MLD patients
- Jennifer Payne – patient with PKU
- Roy Zeighami – father of a Sanfilippo syndrome patient
- Andrea Smith – mother of a MELAS-like syndrome and Type B pyruvate carboxylase patient

FDA Panel

- Julie Beitz (Office of Drug Evaluation III, CDER)
- Donna Griebel (Division of Gastroenterology and Inborn Error Products (DGIEP), CDER)
- Teresa Buracchio (DGIEP, CDER)
- Larry Bauer (Rare Disease, CDER)
- Ron Farkas (Division of Neurology Products, CDER)
- Rachel Witten (Office of Cellular, Tissue and Gene Therapies, CBER)
- Lynne Yao (Pediatric and Maternal Health Staff, CDER)
- Theresa Mullin (Office of Strategic Programs, CDER)

Appendix 3: Meeting Polling Questions

The following questions were posed to in-person and web meeting participants at various points throughout the June 10, 2014 inborn errors of metabolism Patient-Focused Drug Development meeting. Participation in the polling questions was voluntary. These results were used as a discussion aid only and should not be considered scientific data.

Patient-Focused Drug Development for Inborn Errors of Metabolism: Polling Questions

Demographic Questions

1. Where do you live?
 - a. Within Washington, D.C. metropolitan area (including the Virginia and Maryland suburbs)
 - b. Outside of the Washington, D.C. metropolitan area
2. Have you/your loved one been diagnosed as having an inborn error of metabolism (IEM)?
 - a. Yes
 - b. No
3. What is your/your loved one's age?
 - a. 0 – 2
 - b. 3 – 9
 - c. 10 – 17
 - d. 18 – 34
 - e. 35 – 49
 - f. 50 or greater
 - g. My loved one is deceased.
4. Are you/Is your loved one:
 - a. Male
 - b. Female

Question for Topic 1

5. Which of the following symptoms currently have a significant impact on your/your loved one's daily life? Choose all that apply.
 - a. Motor deficits (such as weakness, spasticity, walking problems)
 - b. Balance or coordination problems
 - c. Seizures
 - d. Sensory impairment (such as vision or hearing loss)
 - e. Impaired cognition or developmental delay
 - f. Behavioral problems (such as hyperactivity, hypersensitivity or aggression)
 - g. Bowel or bladder problems
 - h. Pain, such as headaches, nerve pain, or abdominal pain
 - i. Others, not mentioned

Questions for Topic 2

6. What therapies have you used to manage your/your loved one's condition? Check all that apply.
 - a. Dietary restrictions, dietary supplementation or medical foods
 - b. Enzyme Replacement Therapies, such as Elaprase or Naglazyme
 - c. Bone marrow or organ transplantation
 - d. Other prescription medications, such as anticonvulsants or psychiatric medications
 - e. Non-drug treatments, such as dialysis, gastrostomy tubes or splinting/bracing
 - f. Use of assistive technology, such as wheelchairs, walkers or readers
 - g. Other therapies, such as behavioral, physical or occupational therapy
 - h. None of the above.

7. Have you /your loved one ever participated in any type of clinical trial studying experimental treatments for IEM?
 - a. Yes
 - b. No
 - c. I'm not sure

8. If you / your loved one (if you are the guardian) had the opportunity to participate in a clinical trial to study an experimental treatment, which of the following best describes your thoughts?
 - a. **Yes:** It would depend on many factors, but I am generally willing to consider participating
 - b. **No:** I would probably not consider participating
 - c. **Maybe:** I am not sure whether I would be generally willing to consider participating or not