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

Sickle Cell Disease

Public Meeting: February 7, 2014
Report Date: October 2014

Center for Drug Evaluation and Research (CDER) and
Center for Biologics Evaluation and Research (CBER)
U.S. Food and Drug Administration (FDA)

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Introduction

On February 7, 2014, FDA held a public meeting to hear perspectives from patients with sickle cell disease, caretakers, and other patient representatives on the most significant effects of their disease and available therapies. FDA conducted the meeting as part of the agency's Patient-Focused Drug Development initiative, 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 between Fiscal Years 2013 - 2017, each focused on a specific disease area.

Overview of sickle cell disease

Sickle cell disease refers to a group of genetic disorders in which a patient's red blood cells undergo a change of shape known as sickling. This shape change disrupts the normal flow of the red blood cells through the blood vessels of the body, ultimately preventing tissues from receiving adequate oxygen. Sickle cell disease affects approximately 100,000 people in the United States and millions of people worldwide. The disease occurs in 1 of 500 African-American births and in 1 of 36,000 Hispanic births. There are several different genetic variants of sickle cell disease, and disease complications and severity can vary widely across the disease spectrum.

Sickle cell disease can affect every body system. Most patients experience both chronic and episodic pain, and acute pain crisis is the most common reason for emergency department use by patients with sickle cell disease. Other complications of sickle cell disease include susceptibility to infection, stroke (more common in children than adults), acute chest syndrome, fatigue, difficulty concentrating, leg ulcers, priapism (unwanted painful erection), delayed growth and sexual maturation, and pregnancy complications. Over time, blood vessel damage and reduced blood and oxygen flow can lead to avascular necrosis, pulmonary hypertension, vision and hearing problems, kidney dysfunction, cardiovascular diseases, and other effects. The impact of sickle cell disease varies from person to person. Some patients have frequent crises and severe disability, while others are able to lead relatively normal lives.

Therapies to prevent the complications of sickle cell disease are limited and include hydroxyurea, chronic blood transfusions, and bone marrow or stem cell transplantation. These therapies vary in their effectiveness and are associated with serious risks and tolerability issues. Pain crisis management is largely supportive with a combination of hydration, oxygen, anti-inflammatory agents, and pain medications. Other therapies such as antibiotics and vitamin supplements are used routinely for prophylaxis against specific types of infection and to help with making new red blood cells, respectively. New approaches to treating sickle cell disease are being explored, including new medications, advances in transplantation, and gene therapies.

Meeting overview

This groundbreaking meeting gave FDA, other federal officials, and the pharmaceutical industry a unique opportunity to hear directly from patients, caretakers, and other patient representatives about their experiences with sickle cell disease and its treatments. Discussion focused on two key topics: (1) the effects of sickle cell disease that matter most to patients and (2) patients' perspectives on treatments

for sickle cell disease and on clinical trial participation. The discussion questions (Appendix 1) were published in a Federal Register notice that announced 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. An FDA facilitator led the discussion, and a panel of FDA staff (Appendix 2) asked follow-up questions. Participants who joined the meeting via live webcast (referred to in this report as web participants) were also able to contribute comments. In addition, 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 and how many participants shared a particular perspective on a given topic.

Approximately 100 patients with sickle cell disease or patient representatives attended the meeting in-person, and approximately 40 patients or patient representatives provided input through the live webcast. The participation rate was considered high for a meeting on a rare disease. According to their responses to the polling questions, in-person and web participants represented a range of ages. The perspective of patients less than 18 years of age appeared to be represented primarily by caretakers. The majority of participants reported receiving most of their sickle cell care by a hematologist, and most reported having to go to the hospital or emergency room at least once in the past year because of sickle cell disease. Although participants at this meeting may not fully represent the population living with sickle cell disease, the input reflects a range of experiences with its symptoms and treatments. The meeting was also attended by representatives from FDA and other government agencies, industry representatives, researchers, and healthcare professionals.

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 April 8, 2014. 41 comments were submitted to the public docket, the majority by individual patients with sickle cell disease or their caregivers.

More information, including the archived webcast and meeting transcript, is available on the meeting website: http://www.fda.gov/forindustry/userfees/prescriptiondruguserfee/ucm370867.htm.

Report overview and key themes

This report summarizes the input provided by patients and patient representatives at the meeting or through the webcast. It also includes a summary of comments submitted to the docket, beginning on page 18. To the extent possible, the terms used in this summary to describe specific sickle cell disease health effects, impacts and treatment experiences reflect the words used by participants or docket commenters. This report reflects the content of the meeting and docket comments as they relate to patient perspectives on disease symptoms, impacts, and treatments. The report is not meant to be representative of the views and experiences of the entire sickle cell disease patient population or any specific group of individuals or entities. There may be symptoms, impacts, or treatment experiences that are not mentioned in the 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 patient input summarized in this report underscores the serious nature of sickle cell disease, the complexity of treatment, and the broader challenges patients face in getting the care and support that they need. Several key themes emerged:

- The health effects of sickle cell disease are wide ranging. Participants described the excruciating, incapacitating effects of episodic pain crises and acute chest syndrome. They also highlighted the pervasive effects of chronic pain, fatigue, cognitive effects, and temperature sensitivity. Older participants described the debilitating impacts stemming from progressive damage to blood vessels, organs, tissues, and bones. Women shared their experiences with (or fears about) pregnancy. Participants young and old expressed their fear about dying early from their disease.

- Sickle cell disease affects all aspects of patients' lives. The debilitating symptoms and complex treatment needs limit their ability to perform in school, pursue careers, have a family, and maintain relationships. The disease takes an emotional toll as patients face challenges with the healthcare system, stigma within society, financial hardships, and worry about their future. Both young and old live with constant reminders that they are not able to live a normal life.

- Participants described the significant role and benefits of treatments such as hydroxyurea, transfusions, and transplants in managing their disease and its complications. Some participants highlighted how hydroxyurea has positively changed the course of their disease by decreasing the number of sickle cell disease related pain, acute chest syndromes, and hospitalizations. However, these treatments do not work for everyone and they carry significant risks and burdens. Treatment decisions are complex, highly individualized, and depend on the patient's symptoms and severity, response and tolerability to treatments, perspectives on treatment risks, access issues, and other factors such as the ability to find a transplant donor match.

- Participants highlighted the need for treatments that better address (a) the "upstream" causes of sickling and anemia, (b) the daily fatigue and cognitive effects, and (c) the long-term progressive damage of sickle cell disease. They also stressed the importance of taking a holistic approach to managing sickle cell disease that addresses hydration, diet, psychosocial and mental health, and lifestyle changes in addition to medical treatments.

- Participants generally recognize the importance of clinical trials in furthering the development of treatments for sickle cell disease. The majority of participants indicated that they would be willing to consider participating in clinical trials. However, they have questions about potential serious or long-term risks and the specific health benefits they might expect. Participants want more clear, detailed, and transparent information to help them balance the benefits and risks. They stressed the need to increase patients' and healthcare providers' awareness of clinical trial opportunities, and highlighted the potential of community networks and social media. They also stressed the need to establish more trust and respect between researchers and patients.

- The challenges in adequately managing sickle cell disease are much broader than the availability of medical treatments. Participants highlighted the difficulties in having their condition recognized or their symptoms taken seriously, navigating the healthcare system, interacting with healthcare professionals, getting access to treatment, and getting needed accommodations within their schools or workplaces. A few participants highlighted their positive experiences with their healthcare team and with sickle cell centers that can be used to quickly access care.

The input generated through this Patient-Focused Drug Development meeting strengthens our understanding of the burden of sickle cell disease on patients and their experiences and perspectives on treating sickle cell disease. FDA staff will carefully consider this input as it fulfills its role in the drug development process, including when advising sponsors on their drug development programs and when evaluating products for marketing approval. For example, Appendix 4 shows how this input may directly support our benefit-risk assessments for products under review. This input may also be of value to the drug development process more broadly. For example, the report may be useful to drug developers as they explore potential areas of unmet need for patients with sickle cell disease. It could also point to the potential need for development and qualification of new outcome measures in clinical trials.

Topic 1: The Effects of Sickle Cell Disease That Matter Most to Patients

The first discussion topic focused on patients' experiences with symptoms and complications of sickle cell disease and the resulting impacts these health effects exert on patients' daily life. In order to separate potential differences between pediatric and adult experiences, the discussion was segmented to hear first from children and young adult patients (age 23 and younger) and their caretakers, followed by adult patients (older than age 23).

Pediatric and young adult perspective on the effects of sickle cell disease

Four panelists provided comments to start the dialogue on the effects of sickle cell disease in young patients. The panel included two parents and one grandparent, whose loved ones ranged from 10 years to 16 years of age. The fourth panelist was a young adult 23 years of age. The panelists described in depth the challenges facing young people living with sickle cell disease, including acute pain crises and other serious complications such as stroke and acute chest syndrome. They also described their more pervasive, daily struggles with concentration, pain management, and physical activity. In the large-group facilitated discussion that followed the panel discussion, nearly all patients and patient representatives in the audience indicated by a show of hands that their experiences (or those of loved ones) were reflected in the panelists' comments.

In a polling question (Appendix 3, Q7), participants were asked to identify up to three symptoms (excluding pain crisis)[2] that have the greatest impact on their or their loved one's life (from the pediatric perspective). Difficulty concentrating, chronic daily pain, and acute chest syndrome received the highest number of responses. Web participants had similar results, reporting chronic daily pain, fatigue,[3] and difficulty concentrating as their top three symptoms. The discussion revealed the degree to which these effects may be interrelated, such as when fatigue results from sleep disturbances caused by pain, or when cognitive effects are exacerbated by pain or fatigue. The range of symptoms discussed by in-person and web participants is described in more detail below, followed by a summary of their input on the broader impacts sickle cell disease has on children's and young adults' daily lives.

[2] Acute pain crisis was not included in this question because it was assumed that acute pain crises is one of the most significant effects for most patients with sickle cell disease. The intent of the question was to identify effects beyond pain crisis.

[3] Fatigue was included as a response option in the web polling question but not in the in-person polling question.

Pain crisis and chronic pain

Acute pain crises and chronic pain clearly surfaced as one of the most debilitating effects on young patients' lives, affecting them physically and emotionally. Participants described pain crises as unpredictable, sudden episodes of sharp and excruciating pain that frequently require a trip to the emergency room and often leave the child unable to function or sleep. Participants described how a pain crisis makes it difficult to function, interrupts the child's life, and causes stress and anxiety. Some participants also commented on living daily with chronic pain. They described a constant, aching pain with occasional periods of sharper pain. The following examples illustrate the experiences shared in discussion of pain in pediatric patients.

- "The pain can be anywhere in [my son's] body, but usually in his back or his limbs. The severity ranges from mild dull aches to sharp and excruciating pain, but until it's well managed, it can be difficult to perform the tasks of daily living."

- "[My] child who is generally happy and curious began to slow down and ache with pain [and] became so weak that he couldn't manage the stairs in his house."

- "My average day consists now of a Level 7 of pain at least… a constant pain I can't get rid of."

- "When a pain crisis is brewing, [my child] is very edgy, she's very nervous, she's very tearful."

- [When I'm in an acute crisis], I just want to sleep [because] it's that moment of peace you get when you're sleeping that you're not in pain."

A few participants described their crisis triggers, including bumps or falls and stress. Cold weather was highlighted as a particular challenge due to its effect on blood flow resulting in pain. Participants described their attempts to prevent crises by avoiding cold weather or water, staying hydrated, limiting physical activity, being cautious, and trying to minimize stress. When asked by FDA whether participants experienced fatigue as a crisis trigger, many participants appeared not to perceive this relationship; however one participant described experiencing "an instant fatigue that may lead to a pain crisis," and a web participant commented that "fatigue is a sign of my son going through hemolysis leading to possible pain crises."

Fatigue

Many participants identified fatigue as one of the most significant effects of sickle cell disease on their or loved one's daily life. Although it was not included as an option in the in-person polling question (Appendix 3, Q7), many participants indicated that they had included fatigue in their "Other" response. The majority of responding web participants identified fatigue as one of their top 3 health effects. Participants described getting tired during physical activities or feeling "a heaviness that comes over your body." For example, one participant said that most days after school, "the only thing [my son] wants to do is take a nap." A few participants described periodic episodes of severe and debilitating fatigue. For example, a web participant stated that once regular menstruation cycles occurred she "began experiencing great bouts of fatigue."

Cognitive effects

Difficulty concentrating and other cognitive effects associated with sickle cell disease received much attention during the facilitated discussion. Participants described their or their loved one's difficulties being mentally present, focusing, and retaining information. They commented that these effects have a direct impact on the child's school performance. For example, a web participant said that her son "constantly complains of [difficulty] remembering tasks and facts in school." Some participants said that these effects occur independently of their other symptoms, and others identified them as symptoms that occurred in conjunction with pain, fatigue, or difficulty sleeping.

Other symptoms discussed

- Many participants identified **acute chest syndrome** as one of their top three most significant health effects for their child, describing the resulting pain, anxiety, and need for hospitalization. A few participants also commented on asthma and other lung problems. For example, one participant described how her child can get a cold, which triggers acute chest syndrome, which then triggers asthma. Another said that her greatest fear for her child once he becomes an adult is pulmonary hypertension, because "he has had so many episodes of acute chest syndrome."

- Some participants commented that **stroke and silent infarcts** have had a severe effect on their loved one, resulting in permanent damage. One participant described her grandson's stroke at 9 months old, which "left him partially paralyzed on his right side [and he] now walks with a severe limp and has difficulty grasping things with his right hand." Another participant described a "series of silent infarcts culminating [in] a pretty major stroke when [my son] was nine [years old]." She said that the impact on her son was severe, and that he still "has difficulty with walking without assistance and takes a number of meds to control seizure activity."

- A few participants commented that **hearing loss** may be an overlooked symptom in pediatric patients. One participant noted that "even after having tubes placed in [his ears] and his hearing restored, he still struggles [with] speech."

- A few participants commented on **depression and anxiety**, as a result of difficulty in managing symptoms, worry for the future, and social difficulties due to their condition. One parent described a breakdown that her child had during a crisis, saying "I had never seen her as dismayed in my life. Her eyes were glazed over with pain."

- A few participants identified nausea and other **side effects of treatment** as among the most significant effects on their daily life. Treatment side effects are discussed in more detail in Topic 2.

- **Other symptoms** included insomnia, infections, and priapism (prolonged, painful erection). Web participants also commented on jaundice, allergies, and eyesight problems.

Broader impacts on children and young adults

Participants described in detail the broader impact that sickle cell disease has on their or their loved one's daily life, in particular:

- **The ability to attend and perform at school**. Participants described the toll that missing, often unpredictably, days or weeks at a time has on their ability to keep up in school. As one participant commented, her son "missed critical building blocks that caused him to have difficulties in reading early on." Another participant explained her daughter's anxiety in "anticipation of a pain crisis [because] of the enormous amount of back work that she will have when she gets back to school." Participants also described the overwhelming social and emotional toll of missing school, for example: "When [my daughter] returns to school, her friends have moved on with life."

- **Receiving adequate medical treatment and other support.** While some participants highlighted some of the positive experiences they have had with their treatment providers, others described the difficulties in working with healthcare professionals, teachers, school administrators, and others who do not understand or even recognize their child's condition. They stressed the significant impact that these challenges have on their children's health and well-being. For example, one participant described a time when her son experienced a silent infarct at school that went unnoticed because "he was deemed being unruly when he was in the nurse's office… and was sent back to class." A few described specific challenges in obtaining support at school, particularly in accommodating long and sudden absences from school. Participants' comments on challenges associated with health care are revisited below in the Topic 2 discussion.

- **The ability to be like other children**. As one participant explained, "Whenever I pick up [my grandson] from school, the other kids are running around the track and [he] is limping after them or sitting on a bench." Another participant described her son's frustration at having to stay indoors when the weather is cold. Another described a child who was not allowed on a sports team and commented that "bullying is another issue, and that's why children with sickle cell disease want to hide it, because they don't want other people to know that they're different."

- **Worry about their future**. Young patients and caretaker participants expressed their concerns about the long term effects of sickle cell disease, challenges in transitioning to adult care, the cumulative effects of their sickle cell treatments, and of dying early. They also voiced concern about their ability to finish school and start a career or family, in addition to living with the long-term social and emotional impacts of sickle cell disease.

- **Impact on families.** A few participants stressed the impact that the disease, for example the unpredictable nature of pain crisis, has on the family's ability to work, make plans, or take vacations. One participant described sickle cell disease as being "emotionally draining for the child and for the family."

Adult perspective on the effects of sickle cell disease

The meeting discussion continued with an exploration of the adult perspective on the most significant effects of sickle cell disease. In order to focus the discussion, FDA asked adult participants to consider how their symptoms and impacts have either changed or stayed the same as they get older. Four patients with sickle cell disease, ranging in age from 30 to 68, shared their experiences to begin this discussion. Their comments highlighted the life-long reality of sickle cell disease, describing the constant reminders that they are "not able to live normally," the progression of effects as they get older, and their fears about the future. At the same time, they expressed pride in themselves as survivors and hope for the future.

A number of health effects described in the adult discussion mirrored those identified in the pediatric discussion. Chronic daily pain and fatigue received, by a wide margin, the highest number of responses to both the in-person and web polling question (Appendix 3, Q8) that asked adult participants to identify their most significant symptoms. The following are highlights of their comments on these symptoms.

- **Acute pain crises and chronic pain** again clearly emerged as one of the most significant effects facing adults living with sickle cell disease. Participants pinpointed specific crisis episodes so severe that they required months in the hospital followed by rehabilitation. One participant commented that at its worst, "[t]he pain has complete control to the point that three times in my life I prayed to God to let me die because I didn't think I could take any more pain." A few participants described living with constant pain even when not in crisis. For example, one participant noted "intense bone pain, not crisis pain… that is due to the complication of sickle cell disease." Participants commented that acute or chronic pain often exacerbates other symptoms including fatigue, insomnia, difficulty concentrating, and mobility issues.

- **Fatigue** also emerged as a significant effect facing many adults. Participants described experiences ranging from general daily tiredness to episodic severe exhaustion. For example, one participant described times where she was fatigued to the point of not being able to move, and needed to sleep all day. She explained that these episodes did not have a consistent pattern and were not related to pain or hospitalizations. Some participants discussed insomnia and other sleep difficulties in conjunction with fatigue. For example, a web participant described being "tired and feeling like a dead weight. Your mind is racing but your body won't cooperate." Another participant described a "vicious cycle of insomnia which further aggravates fatigue."

- A few participants stated that **difficulty concentrating and other cognitive issues** have not dissipated as they got older. One participant expressed her frustration with retaining information, organizing thoughts, and communicating, which she and her healthcare provider believe are associated with her underlying sickle cell disease.

- Adult participants reiterated their sensitivity or **intolerance to cold temperature or weather changes**. For example, one participant described a pain crisis that lasted for two days after being doused with cold water, and explained that "when the cold gets into your bones, it's just like serious pain."

A wide range of health effects, particularly those associated with more progressive or long-term complications of sickle cell disease were discussed in much greater detail in the discussion focused on adult experiences. Some participants identified these long-term complications as what they fear most about their disease. For example: "I can deal with the pain, but what… I'm most concerned about is the

fact that my organs are dying, my tissues are dying, every time I'm having a sickle cell episode."

The effects that received the most attention in this discussion are summarized below:

- **Cardiovascular events**. In addition to strokes and infarctions described in the pediatric discussion, many adult participants commented on a number of longer-term cardiovascular issues, including pulmonary hypertension, pulmonary embolism, and heart failure. For example, one participant described having pulmonary hypertension since age 20, which "has taken a devastating toll on my life, period. I have to have oxygen all the time, [and] with sickle cell, you're already oxygen deprived."

- **Organ damage.** Several commented on experiencing damage resulting from long-term effects of restricted blood flow and necrosis, often resulting in organ failure or removal. Specific examples include kidney failure, spleen or gallbladder removal, hernia, stomach ulcers, and lung thoracotomy.

- **Chronic leg or skin ulcers**. For example, one participant commented that of all the symptoms her adult son experiences, ulcer wounds "have really caused the biggest problem for him."

- **Bone and other osteopathic disorders**, including avascular necrosis, herniated disc, deteriorating rotator cuff, compression fractures, and hip replacement. Participants who commented on these effects described intense, chronic pain.

- **Hearing loss.** For example, one participant indicated that he has lost 80% of the hearing in his left ear and 30% in his right ear, and he considers hearing loss to be among his greatest concerns. A web participant described chronic ear infections which led to hearing loss.

- **Loss of sight and other eye issues**. For example, one participant described almost losing vision due to sickle cell retinopathy, which required surgery.

- **Pregnancy complications.** The mother of twins described her experience with pregnancy, which included seven major crises, placental complications, intense bone pain, and swelling: "My doctors… said that I needed to have a selective abortion … [but then] decided [on an] exchange transfusion, and I was able to carry my babies to 36 weeks 4 days." A few participants commented on other reproductive health issues such as miscarriages, ectopic pregnancies, and uterine crisis which resulted in menopause and infertility at age 20.

- **Complications of long-term sickle cell treatment** were identified as being among the most significant effects for a few participants. Treatment side effects are discussed in more detail in Topic 2.

- **Other symptoms** mentioned include asthma, chronic bronchitis, priapism, gout, sinusitis, allergies, migraines, brain aneurism, jaundice, oral or dental pain, and tooth loss.

Broader impacts of sickle cell disease (adult perspective)

Adult participants also depicted the broader impact that sickle cell disease has on their daily life. Much of their input echoed the impacts described in the pediatric discussion. These impacts include:

- **Managing work and careers,** including unpredictable and lengthy absences, struggling to keep up at work, or not being able to work at all. For example, one participant described the stress in managing "all the doctor appointments, medications, different treatment options, things like that, and work a full-time job and, you know, live." One participant shared devastation at being "told that I could not be a chef anymore."

- **Caring for themselves and their families.** One participant depicted how difficult it is for her as a mother, saying: "Most of my days are spent lying in bed unable to get out of bed … I am often late taking [my children] to school because I'm just having a lot of pain."

- **Maintaining relationships**. For example, one participant explained: "I can deal with the pain. Not being able to take the person I am with to dinner because my joints are aching, that's really what I go through with sickle cell disease."

- **Concerns about their future health,** particularly regarding their condition progressing before better treatments are available. Participants also commented on their concerns with passing on the sickle cell trait to their offspring.

- **Emotional impacts**. Participants described the emotional toll of living with symptoms, dealing with the healthcare system (discussed more in Topic 2), managing their finances, and battling the stigma of their disease. For example, one participant shared her feelings of isolation growing up: "there were very few blacks, and I was the lone child in the community with something strange." Another described "the emotional toll of having a disease that many people were taught to be ashamed of." A few participants expressed feelings of hopelessness and despair: "Who wants to hear that they may not make it past the age of 18…. not be able to have children…. not be able to graduate college because they have sickle cell disease…?"

Topic 2: Patient Perspectives on Treatments for Sickle Cell Disease and Participation in Clinical Trials

The second discussion topic focused on patients' experiences with therapies used to treat their condition. Six panelists provided comments to start the dialogue; five were adult patients and one was the parent of a child with sickle cell disease. Panelists shared their experiences with complex treatment regimens, including a variety of prescription and over the counter medications, medical procedures, alternative therapies, and lifestyle changes. The panelists described their struggle in finding long-term effective and tolerable therapies that would help them lead normal lives.

In the large-group facilitated discussion that followed, experiences voiced by participants largely reflected the comments shared by panelists. Participants described in detail the benefits and downsides they or their loved ones have experienced in their treatment regimens, what their ideal therapy for sickle cell disease would address, and their perspectives on clinical trials. Their comments on each of these topics are summarized below.

Sickle cell disease treatments

Participants reported using a wide range of therapies, often in combination, to prevent sickle cell disease complications or to address specific symptoms. Not all of these treatments were discussed in detail. The following is a summary of the input on those that were discussed in more detail.

Hydroxyurea

Hydroxyurea, a key component of care for many patients with sickle cell disease, was the drug most frequently discussed during this meeting. Several participants correlated successful use of hydroxyurea with a significant decrease in the number of pain crisis episodes and other sickle cell symptoms. For example, one participant said she has been able to avoid hospitalizations due to pain crises for the past 3-1/2 to 4 years through the combined use of hydroxyurea and another medication used off-label. Another participant commented that hydroxyurea has helped reduce the occurrence of acute chest syndrome in her 13-year-old son; since starting the drug at age 6, he has only had one acute episode, compared to the eight episodes he had from age two to six.

In contrast to the positive experiences discussed, some participants described less positive experiences and difficulty balancing the benefits and risks of hydroxyurea. For example, one participant had to reduce his dose of hydroxyurea from 2,500 milligrams because the higher dose had resulted in the exacerbation of kidney disease. Another participant commented on experiencing paralysis when first attempting the use of hydroxyurea, and thus avoided the treatment for years. Other side effects described included hair loss and fingernails turning black. A few participants described being a "non-responder" for hydroxyurea, or experiencing decreased effectiveness from the drug over time. A few others expressed concern about the drug's potential toxicity and believed that the unknown long term risks of taking hydroxyurea are not worth its benefits. As one participant explained, "I took myself off [hydroxyurea] when I was an adult because at the time the doctors couldn't tell me the long-term effects of taking the drug. I don't want to substitute sickle cell for another disease that I know nothing about."

Blood transfusions/blood exchanges

More than half of all participants indicated that their sickle cell treatment includes blood transfusions and exchanges. Although participants appear to view these procedures as critical to disease management, their comments focused on the treatment downsides. They described complications from frequent line insertions, including pain, scarred veins, and a resulting need for an intravenous port, which can be painful and become clogged. A few participants discussed challenges associated with the development of antibodies to blood types used in transfusions, which limits future accessibility of certain blood types, increases the risk of immune system reaction, pulmonary embolism, and pregnancy complications. For example, one participant described suffering a miscarriage that her healthcare team attributed to her use of "whole body transfusions." Another participant described swelling "like a Michelin Man" after a transfusion.

Bone marrow transplants

A few patients and patient representatives spoke in detail about their experience with bone marrow transplantation, including the decision to undergo the procedure, finding a matching donor, surgery complications, and recovery. A few participants described positive experiences and believed that the transplant has led to significant improvements in quality of life. For example, one participant described a patient who was previously unable to exercise without experiencing pain episodes, who has since

improved his ability to exercise and is now seeing positive physical results. A web participant, a 14-year-old sickle cell patient, described her bone marrow transplant as “very successful.”

Some participants, however, described having much less success with bone marrow transplantation due to the difficulty in finding matches, transplant rejection, or other complications. Regardless of negative experiences, participants conveyed positive views about bone marrow transplants for themselves and others in the future. For example, a participant commented on considering a bone marrow transplant for his adolescent son because “at this point [we] have decided that that's the only thing that we hold out hope for... as far as we know, the bone marrow transplant is the only cure.”

Iron chelators

Iron chelators, which address iron overload associated with blood transfusions, were discussed frequently at the meeting. Discussion touched upon two types of medications: an injection product, called Desferal (desferoxamine), and an oral product called Exjade (deferasirox). Participants who discussed Exjade attested to the drug’s effectiveness and convenience of self-administration. As one participant explained, “we're very thankful because otherwise he would have to be in the hospital hooked up to an IV in order to chelate. This he just does at home, and he hasn't had any ill effects.” Others agreed that Exjade was effective but said that the side effects they experienced outweighed the benefits. One participant reported noticeable hearing loss after beginning treatment, which caused her to discontinue use and switch to Desferal. Other side effects of Exjade mentioned included burning during ingestion, auditory and visual hallucinations, stomach complications, and tinnitus (ringing of the ears). Participants who commented on their use of Desferal generally said that that they experienced fewer side effects than Exjade. However, one web participant said that she experienced many side effects, including a burning sensation from the Desferal injection.

Pain relievers

Specific treatments for pain were not discussed in depth at this meeting. However, in response to polling questions (Appendix 3, Q9 and Q10), about three-fourths of participants indicated they take prescription pain medications and more than half indicated that they take over-the-counter pain meds. By a show of hands, many of these participants indicated that they take pain medications every day or almost every day. Drugs mentioned included naproxen, hydrocodone, hydromorphone, oxycodone, OxyContin, and morphine. While participants acknowledged the importance of pain relievers in helping them to manage pain, they expressed varying degrees of effectiveness. One participant commented that she “has not come across anything that really does a great job on the pain.” Some participants recognize the effectiveness of pain relievers but choose not to use them in order to avoid the drugs’ cognitive side-effects, propensity to cause drowsiness, and potential for abuse. For example, one participant said, “I cannot take pain meds because I need to be present and be able to raise my kids.” A few participants stressed the challenge in accessing pain medications (discussed in more detail later in this section).

Other drug treatments

Other drugs and medical procedures mentioned included intravenous fluids, folic acid, antibiotics, antihistamines, ACE inhibitors, supplemental oxygen, and various surgeries.

Non-drug therapies

Participants emphasized the importance of practicing holistic care in preventing or managing sickle cell disease symptoms. Specific therapies or practices mentioned included:

- Alternative therapies, including cupping, acupuncture, massage therapy, TENS units (devices that use electric currents to stimulate nerves), heat therapy, aromatherapy, and topical oils to treat line incisions.

- Adequate hydration and diet, including eating a diet rich in natural organic ingredients and plenty of green vegetables and fruits, as well as eating a low sodium diet or avoiding iron-rich foods. One patient noted, "I have noticed a very strong correlation with not only what I eat but when I eat it and how I feel the next day."

- Supplements, beside folic acid, included men's vitamin pills and prenatal vitamins. Other supplements included dandelion tea, Vitamin B-12 for energy, L-arginine, and L methionine for "slowing the sickling cycle."

- Stress management, including art therapy, yoga, Tai Chi, and faith and prayer.

Perspectives on an ideal treatment

Participants were asked to consider what they might look for in an ideal treatment for sickle cell disease. They raised a number of priorities, including:

- Treatments that better target the underlying disease. One participant noted that current treatments focus on the "downstream" effects of sickle cell disease, such as pain and iron overload, and she emphasized the need for treatments to address "upstream" sickle cell issues such as the duration of sickling events and the underlying anemia.

- Treatments that can help prevent long-term complications or reverse the damage of complications like stroke. As one participant explained, "Nothing addresses the tissue damage that's occurring with every single crisis."

- Treatments that patients can self-administer. One participant suggested that emergency room visits could be reduced if there were more effective therapies that patients could administer themselves, such as IV or oxygen therapy, This participant noted current "fear from the medical community" about potential misuse or abuse, but believed that "with proper education and training, [patients] could handle a lot of things at home."

- Treatments that "stop a pain crisis in its tracks."

- Medications that address fatigue, cognitive effects, and anxiety.

- Holistic treatments that address psychosocial, stress and mental health issues. One participant stated that "we have a lot [of treatments] that are compartmentalized… I would like to see some systematic comprehensive strategies to address the whole person."

- Medications that have fewer side effects and serious risks. As one participant explained, “we're suffering from sickle cell, we don't want to suffer from [any] side effects other than what we've been dealt with.”

- Improved healthcare more broadly (discussed further below in *Broader issues with sickle cell disease treatment*)

Perspectives on participating in clinical trials

FDA was particularly interested in learning patients’ and caretakers’ perspectives on participating in clinical trials for potential new sickle cell disease treatments. This included finding the best way to communicate with patients with sickle cell disease about clinical trial opportunities. According to a polling question (Appendix 3, Q11), almost half of all respondents had previous experience participating in a clinical trial. Participants’ comments on participating in clinical trials and on communicating about clinical trials are summarized below.

Considerations on clinical trial participation

To help guide the discussion, participants were asked to imagine a scenario (see full text in Appendix 3) in which they (or a loved one) were given the opportunity to participate in a clinical trial to study an experimental treatment for sickle cell disease. This hypothetical treatment may decrease the number of pain crises or hospitalizations in some people, but has common side effects as well as rare but more serious treatment risks. The hypothetical clinical trial involves four clinic visits over a one year period.

Participants were asked to comment on what first thoughts or questions came to mind as they heard this scenario. In response, participants stressed the need for “clear and detailed information” that helps them balance their individual benefits and risks, as demonstrated in the following excerpts:

- "’This drug is expected to help some people.’ … I would want to know exactly how ‘some people’ was determined, what exactly you used to determine who this helps.”

- “We've seen [from our discussion today] that there is a lot of diversity in the symptoms that people have and their experience with sickle cell disease. So if it's a drug that helps people who have ulcers, I might not be the best person for that study.”

- “What's its method of action? ... I need to know not just this is going to help sickle cell but this is going to help treat the persistent acute chest syndrome that you're dealing with by approaching this particular target area."

- “Because of [a very negative experience in the past] I would be more questioning about what is the final result you're looking for, and is it going to help me out in the long run?”

Participants were next asked (Appendix 3, Q12) to identify factors that may be most important to them if they were deciding whether or not to participate in the hypothetical trial. ‘Rare but serious side effects’ received the most responses by in-person and web participants, followed by ‘how the treatment might improve my health.’

Finally, participants were asked to think about whether they would be generally willing to consider participating in the hypothetical clinical trial if given the opportunity (Appendix 3, Q13). The majority of participants indicated that they would be open (answering “yes” or “maybe”) to considering

participation in the hypothetical clinical trial. Several participants stressed the importance of “giving back to society" so that “10 years, 20, 30, 40 years from now there are fewer people sitting in this room trying to address the same issue." A much smaller number of participants indicated that they would “probably not consider participating” in a clinical trial. As one participant explained, “the severity of my disease is not yet to a point where I am bold enough and comfortable enough to be among the first few trials." The overall interest in clinical trial participation was mirrored by the polling results and comments of web participants.

Communicating information about clinical trials

Participants were asked to comment on the best way to communicate information about clinical trials to patients. One participant, a representative of a patient organization, commented that for “most of the people that participate in clinical trials or would be interested in participating in clinical trials, the main gripe that we get is that they don't hear about it.” She explained that for many patients, “their doctors are their trusted source,” but that “their doctors often don’t even know about the clinical trials.” She also commented that few patients visit clinicaltrials.gov, and that those who do have found it “really hard to navigate the site and… figure out what trials they were eligible for and what hospitals were doing the trials.” Other participants agreed, as one explained: “When we do hear about clinical trials, we aren’t given a whole lot of information… why would I want to participate in something where you're not giving me enough information to make an educated decision.”

Participants stressed that social media and community-based networking are important tools for sickle cell disease patient support and advocacy and should play a key role in raising awareness about clinical trials. One participant explained that the sickle cell community is “unlike any other disease I've ever worked with. Most people, they go to clinicaltrials.gov, they go to the doctors, but in this disease specifically, we go to each other.” Other participants agreed, describing learning of clinical trials through their friends, social media, or on media programs that are geared for the black community.

More broadly, however, some participants stressed that the real issue in increasing clinical trial participations is not how the message gets out, but rather is the “trust and the communication between our community and the medical community.” For example, one participant described how her doctor took the time to carefully explain the study and answer all of her questions, “[and] because of that trust factor that I developed in my doctor, I was willing to participate in that study.” However, another participant expressed strong mistrust in clinical research: “I've learned… that just because it says it's a clinical study … does not mean it's going to help you. It's going to help them first and then it's going to help you, if it helps you at all.” Another participant stressed that building trust with patients will require “chang[ing] those dynamics such that our community receives the same respect as the mainstream community in how we're dealt with by the medical community.”

Broader issues with sickle cell disease treatment

Throughout the meeting, participants provided a range of perspectives on the quality of the care they receive as part of their sickle cell treatment. Some described being very satisfied with the care they received; for example, one participant credited his hematologist with saving his life. However, participants stressed that any discussion on the treatment of sickle cell disease must reflect the broader challenges that patients with sickle cell disease face in getting adequate treatment and support. Participants described their difficulties in transitioning to adult healthcare providers from their pediatric care, navigating the healthcare system, interacting with healthcare professionals, and gaining access to

treatment. While participants viewed the discussion on specific therapies and drug development as important, they believed that the other issues with the healthcare system are equally or more pressing.

A major area of concern for some participants was a lack of awareness among some healthcare professionals about sickle cell disease and its treatment. Many participants who sought treatment in the emergency room setting spoke of being treated by hospital staff with disrespect, dismissal, or "differential treatment… based on the color of skin." For example, a few participants described times when their emergencies were not taken seriously, and others commented on being labeled as "drug seekers" and struggling to gain access to needed pain medications. Participants stated that these issues resulted in an increased level of mistrust between patients and the medical community. They stressed the importance of improving hospital staff cultural sensitivity and training on how to identify and treat sickle cell disease. Some participants also described the challenges in finding support from people who understand the experiences they are going through and commented on the importance of having more patient support in the hospital.

A few participants described receiving quality care from their hematology teams or at sickle cell centers. For example, one participant described his very positive experience at a sickle cell infusion center, where there were no wait times and staff members were well versed in the manifestations and treatments of sickle cell disease. This participant believed that more patients should have access to these centers.

Other considerations participants raised included improving diagnosis, addressing the significant costs of treatments, better understanding the disease manifestations of sickle cell trait, and increasing awareness about passing on sickle cell disease.

Summary of Comments Submitted to the Public Docket

41 comments were submitted to the public docket that supplemented the Patient-Focused Drug Development meeting on sickle cell disease. The majority of comments were submitted by adult patients or parents of children with sickle cell disease. Two comments were submitted by sickle cell advocacy organizations; one of these submissions included results of a survey conducted by Genetic Alliance in partnership with five sickle cell disease advocacy organizations (hereafter referred to as the PEER survey). Two comments were submitted by members of the pharmaceutical industry.

The docket comments reflected the experiences and perspectives shared at the February 2014 meeting. They further elaborated on several issues raised during the meeting. The following is a summary of comments provided on sickle cell disease effects, treatments, and clinical trial participation. Particular focus is placed on topics that were not addressed in detail at the meeting.

Submitted comments on symptoms of sickle cell disease

The docket comments emphasized the debilitating nature of sickle cell disease as well as the significant impact it has over the course of a patient's life. The symptoms described were generally consistent with the symptoms raised at the meeting in both the pediatric and adult discussion segments. Pain crisis, chronic pain, general fatigue, sleeping difficulties, cognitive impairments, acute chest syndrome, and issues such as organ and bone damage were all raised by several commenters, who highlighted these symptoms as among the most debilitating effect of sickle cell disease. The PEER survey results also generally aligned with the meeting input; pain and fatigue/tiredness were the most frequently identified

symptoms. Survey respondents also identified weather sensitivity, infections, jaundice, and swelling of hands and feet as their significant issues.

Below are highlights of a selection of frequently mentioned symptoms.

- **Fatigue and/or sleep disturbances** were listed in many comments as being one of the top three symptoms of sickle cell disease that affected daily life. Commenters focused on unrefreshing sleep, difficulty falling and staying asleep, general weariness or fatigue during the day, and tiring quickly from everyday activities. One person described struggling with unrefreshing sleep, saying "It doesn't matter how much sleep I get or how many vitamins I take, exhaustion is a reality." Another explained the burden that dealing with fatigue took by saying that she has to "meticulously manage diet, lifestyle, and sleeping habits" to maintain a job and normal social interactions.

- **Acute chest syndrome** and other forms of breathing difficulty was the third most frequently mentioned symptom in the docket. Commenters described the severity of breathing difficulties as ranging from shortness of breath to near inability to breathe, with more serious cases sometimes requiring intubation. Commenters emphasized the debilitating impact on daily life that acute chest syndrome had for those most severely affected, including disruptive impacts on sleep patterns, inability to perform basic physical activities, and inability to tolerate cold weather.

- **Bone, organ, and tissue damage** resulting from blood circulation issues all received greater emphasis in the docket than at the meeting. Specific symptoms that fell under this category included avascular necrosis, spleen and kidney damage, and necrotic wounds and ulcers on various body parts. Commenters affected by one or more of these issues universally spoke of the significant impact these symptoms had on their lives. One commenter described having had two total hip replacements before age 35. Another spoke about how a chronic leg ulcer had affected her husband's ability to walk. Many commenters identified organ loss or failure as their greatest concern for their health in the future.

Other symptoms mentioned in the docket included increased risks and complications from infections, hearing loss, seizures, heart issues (such as heart palpitations), and cognitive issues.

Submitted comments on the overall impact of sickle cell disease on daily life

The docket comments reiterated the significant and debilitating effect sickle cell disease has on every aspect of patients' lives, throughout their lives. Most commenters emphasized the impact on school and professional life. They described the challenges they faced with missed time due to hospitalization, unsympathetic school and work environments, and poorly equipped medical and nursing staff. From a social perspective, challenges included isolation from peers, inability to participate in common activities, lack of understanding of the disease, and the stigma by people who don't understand their illness.

Other impacts on daily life mentioned in the docket included inabilities to enjoy certain recreational activities, the need to rely on others for personal care at home, emotional impacts such as stress, anxiety, and depression, difficulties with managing family life, and social isolation from peers.

Submitted comments on treating sickle cell disease

The submitted comments reflected the challenges of managing the symptoms of sickle cell disease with limited treatment options. The range of commenters' experiences was similar to those at the public meeting in terms of prescription drug use and their use of non-drug therapies.

The most common therapies mentioned on the docket were hydroxyurea, folic acid, blood transfusions, and antibiotics. The range of perspectives on these treatments demonstrated the variability in treatment success. For example, some described positive experiences with hydroxyurea, while others experienced significant side effects and were not able to use it. Commenters also discussed a range of medications used to manage pain, including opioids and morphine. The most commonly mentioned concern associated with these painkillers was the fear of developing a dependency. General discussion on treatment side effects was limited in the docket; however, the PEER survey respondents identified fatigue, pain, constipation, and insomnia as the most significant side effects. Comments related to non-drug therapies closely resembled input received at the meeting and are not revisited here.

Commenters indicated what they would like to see in an ideal treatment for sickle cell disease. The three most common aspects included: target the underlying sickling of cells to reduce the amount of sickled cells, prevent the onset of pain crises, and prevent long-term complications of sickle cell disease such as organ damage. Better treatments for fatigue and less invasive therapies were also mentioned.

Commenters addressed the subject of clinical trials and shared perspectives similar to those of meeting participants. For example, a large majority of respondents to the PEER survey said that they would either agree or possibly agree to participate in a clinical trial. Docket commenters generally recognized the importance of clinical trials for sickle cell disease, but they balanced this with concern over their personal health and livelihood. They said that they want more information on potential benefits and risks, and wanted to make sure they got information from a doctor or hematologist before deciding.

Finally, many docket comments also reiterated the broader challenges patients with sickle cell disease face in getting proper healthcare. They described their experiences and concerns with finding doctors or hospitals who understand their condition, long waits in the emergency room, "being seen as a drug addict or substance abuser," and more broadly, noticing sickle cell disease as being "relegated to the status of 'only a Black disease.'" Commenters said that these issues with the healthcare system were among their greatest concerns.

Conclusion

This Patient-Focused Drug Development meeting provided FDA an important opportunity to listen to patients, caretakers, and advocates share their experiences and perspectives on sickle cell disease and what matters to them about treatments. More broadly, we believe that this meeting provided this patient community one of the first opportunities to provide their input to the broader set of stakeholders in the drug development and healthcare communities, including government (e.g., National Institutes of Health, the U.S. Centers for Disease Control), healthcare professionals, and the pharmaceutical industry.

We are grateful to all of the participants who thoughtfully and courageously shared their experiences and perspectives. As one participant commented,

> "You have learned a lot about us, we have opened up to you in ways that many of us do not open up to our hematologists, and we've opened up to you in ways that many of our families have never seen us before."

FDA received positive feedback from many meeting participants, including patients, advocates, and industry representatives on the value of this meeting. It was particularly encouraging to hear patients describe the positive impact that the meeting had on them personally, as illustrated in the following comments:

> "This is the first time that I don't feel alone, seeing everyone and hearing everyone's stories."

> "I definitely have fears and worries in regard to my sickle cell, but just watching and listening to the comments that have been said today, I am so proud to be here and be able to listen to people that have actually made it so far… I think it gives all of us hope to let us know that we can make it further than what is expected definitely."

We recognize that patients have a very unique ability to contribute to our understanding of the broader context of the disease, which is important to our role, and that of others, in the drug development process. It is clear that sickle cell disease is a debilitating disease that can severely affect a patient's day-to-day functioning and have a devastating impact on a patient's life. We share the patient community's desire and commitment to furthering the development of safe and effective drug therapies.

Appendix 1: Meeting Agenda and Discussion Questions

Sickle-Cell Disease Public Meeting on Patient-Focused Drug Development

February 7, 2014

9:00 – 10:00 am	**Registration**
10:00 – 10:05 am	**Welcome** Sara Eggers, PhD *Office of Strategic Programs (OSP), Center for Drug Evaluation and Research (CDER), FDA*
10:05 – 10:10 am	**Opening Remarks** Ann Farrell, MD *Director, Division of Hematology Products (DHP), CDER, FDA*
10:10 – 10:20 am	**Overview of FDA's Patient-Focused Drug Development Initiative** Theresa Mullin, PhD *Director, OSP, CDER, FDA*
10:20 – 10:35 am	**Background on Sickle Cell Disease and Treatment** Nicole Verdun, MD *DHP, CDER, FDA*
10:35 – 10:45 am	**Overview of Discussion Format** Sara Eggers, PhD *OSP, CDER, FDA*
10:45 – 11:40 am	**Pediatric and Young Adult Perspective on Topic 1**: **The effects of sickle cell disease that matter most to patients** A panel of caregivers and young adult patients will provide comments followed by a large-group facilitated discussion with participants in the audience.
11:40 – 12:30 pm	**Adult (Age 23+) Perspective on Topic 1** A panel of patients and patient representatives will provide comments followed by a large-group facilitated discussion with participants in the audience.
12:30 – 1:30 pm	**Lunch**
1:30 – 1:35 pm	**Afternoon Welcome** Sara Eggers, PhD *OSP, CDER, FDA*
1:35 – 2:05 pm	**Panel Discussion on Topic 2: Patients' perspectives on treatments for sickle cell disease** A panel of pediatric and adult patients or patient representatives will provide comments to start the discussion.

2:05 – 2:50 pm **Large-Group Facilitated Discussion: Topic 2**
Patients or patient representatives in the audience will be invited to add to the dialogue.

2:50 – 3:20 pm **Patient perspectives on participating in a clinical trial to study experimental treatments**
Patients and patient representatives in the audiences will be invited to contribute to a discussion on Topic 2 Question 5.

3:20 – 3:50 pm **Open Public Comment**

3:50 – 4:00 pm **Closing Remarks**
Kathy Robie-Suh, MD, PhD
DHP, CDER, FDA

Discussion Questions

If commenting on behalf of a child or other loved one who has sickle cell disease, please answer the following questions as much as possible from the patient's perspective.

Topic 1: The effects of sickle cell disease that matter most to you

1) Of all of the ways that sickle cell disease affects your health, which 1-3 effects have the greatest impact on your life? (Examples may include pain crises, breathing problems, difficulty concentrating, tiredness, infections, and others.)

2) How does sickle cell disease affect your life on an "average" day?
Are there activities that you cannot do at all or as well as you would like? Please describe, using specific examples. (Examples may include sleeping through the night, concentrating at work or at school, participating in physical activities, and others.)

3) How does sickle cell disease affect your life on the "worst" days, such as days when you have a pain crisis or have to be hospitalized for some reason?
Are there activities that you cannot do at all or as well as you would like? Please describe, using specific examples.

4) What worries you most about how sickle cell disease could affect your health in the future?

5) What specific concerns do you have about sickle cell disease:
In infants and young children?
In adolescents and young adults?
In older adults?

Topic 2: Perspectives on treatments for sickle cell disease

1) Are you currently using any prescription medicines or medical treatments to prevent or treat any negative effects of your sickle cell disease? Please describe these treatments, which may include blood transfusions, supplemental oxygen and prescription medications such as hydroxyurea, antibiotics, pain medications, and others.

How well do these treatments work for you? For example, how well do they reduce your number of pain crises, hospitalizations, or strokes? How well do they help you manage your pain, breathing difficulties, or other health effects?

What are the biggest problems with these treatments? (Examples may include side effects of medicine, going to the hospital for treatment, frequent blood tests, etc.) How do these problems affect your daily life?

2) Besides prescription medications, what else do you do to prevent or treat any negative effects of your sickle cell disease? Please describe any medications purchased at a store without a prescription, home remedies, diet changes, massages, or other therapies.

What specific parts of your sickle cell disease do these treatments address?

How well do these treatments work for you?

What are the biggest problems with these treatments?

3) What parts of your sickle cell disease do your current treatments not treat at all or not as well as you would like?

4) Assuming that there is no cure for sickle cell disease, what specific things would you look for in an ideal treatment?

5) If you had the opportunity to consider participating in a clinical trial studying experimental treatments for sickle cell disease, what things would you consider when deciding whether or not to participate? Examples may include how severe your sickle cell disease is, how well current treatments are working for you, your concern about serious risks, and other things.

Appendix 2: FDA and Patient Panel Participants

FDA Panelists

Ann Farrell	Division of Hematology Products (DHP), Office of Hematology-Oncology Products (OHOP), Office of New Drugs (OND), Center for Drug Evaluation and Research (CDER)
Nicole Verdun	DHP, OHOP, OND, CDER
Kathy Robie-Suh	DHP, OHOP, OND, CDER
Anne Pariser	OND, CDER
Theresa Mullin	Office of Strategic Planning, CDER
Jonca Bull	Office of Minority Health, Office of the Commissioner
Lisa Faulcon	Office of Blood Research and Review, Center for Biologics Evaluation and Research

Patient Panelists

Topic 1 (Youth Discussion)
Nancy Rene
Andrea Williams
Dawn Nelson
Alana McClinton

Topic 1 (Adult Discussion)
George Carter
Terri Booker
Helen Sarpong
Marqus Valentine

Topic 2
John Moore
Tina Kay
Lakiea Bailey
Olga Barnwell
Anthony Braxton
Moses BunduKarma

Appendix 3: Meeting Polling 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. Which of the following best describes you? Choose all that apply:
    a. I have sickle cell disease
    b. I am a family member or caretaker of someone with sickle disease
    c. I work for a sickle cell disease patient support or advocacy organization
    d. I am a healthcare professional who works with sickle cell disease patients
    e. Other

We ask that the remainder of the questions be answered by the person with sickle cell disease or a caregiver who is commenting on behalf of a child or other loved one who is not answering for himself/ herself.

3. What is your age / your loved one's age?
    a. 0 – 5
    b. 6 – 12
    c. 13 – 17
    d. 18 – 22
    e. 23 – 49
    f. 50 or greater

4. Are you / Is your loved one:
    a. Male
    b. Female

5. How would you describe the place that you/your loved one receive **most of your sickle cell care**?
    a. At a sickle-cell treatment center with a hematologist
    b. Not at a sickle cell treatment center but with a hematologist
    c. A primary care center (family medicine, internal medicine, pediatrician)
    d. Only emergency rooms and hospitals as needed
    e. Not sure

6. <u>In the past year</u>, how often have you / your loved one had to go to the hospital or the emergency room because of sickle cell disease?
    a. No times in the past year
    b. 1 – 2 times
    c. 3 – 5 times
    d. 5 – 10 times
    e. More than 10 times

7. Pediatric perspective: **Other than acute pain crises**, what health effects of sickle cell disease currently have the greatest impact on your / your loved one's life? **Please choose up to 3 effects.**
    a. Chronic daily pain, such as joint pain or hip pain
    b. Multiple infections
    c. Strokes
    d. Acute chest syndrome
    e. Growth problems or delay in reaching puberty
    f. Priapism
    g. Problems with spleen
    h. Iron overload
    i. Difficulty concentrating
    j. Other effects not listed above

8. Adult perspective: **Other than acute pain crises**, what health effects of sickle cell disease currently have the greatest impact on your life? **Please choose up to 3 effects.**
    a. Chronic daily pain, such as joint pain or hip pain
    b. Strokes
    c. Acute chest syndrome
    d. Iron overload
    e. Priapism
    f. Problems with eyesight (from sickle cell disease)
    g. Damage to heart or pulmonary hypertension
    h. Kidney disease or gallstones
    i. Other effects not listed above

9. In the past year, have you / your loved one used <u>prescription medicines or medical treatments</u> to treat sickle cell disease? Check all that apply.
    a. Folic acid
    b. Prescription pain medications
    c. Hydroxyurea
    d. Blood transfusions
    e. Oxygen therapy
    f. Antibiotics
    g. Transplants (such as bone marrow transplants)
    h. <u>Other</u> prescription medicines or medical treatments
    i. <u>No</u> prescription medicines or medical treatments
    j. I'm not sure

10. In the past year, have you / your loved one done anything else to treat sickle cell disease? Check all that apply.
    a. Taken over-the-counter pain medicines
    b. Had a massage or acupuncture
    c. Taken vitamins, dietary supplements, or herbal remedies
    d. Take in extra fluids
    e. Followed a special diet, such as avoiding certain foods
    f. Attended pain programs or support groups
    g. Used some other therapy

h. No other therapies
i. I'm not sure

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

Clinical trial hypothetical scenario:
Imagine that you (or your loved one) have been invited to participate in a clinical trial to study an experimental treatment for sickle cell disease. Early research in animals and people shows that this treatment may decrease the number of pain crises or hospitalizations in some people with sickle cell disease. The purpose of the study is to better understand how well this treatment works and its safety. The study will enroll 1000 participants with sickle cell disease. This clinical study lasts one year, and involves four clinic visits, occurring once every 3 months. More common side effects of this therapy may include nausea, diarrhea, fatigue, headache, and rash. Rarer but more serious side effects may include infection, bleeding, and life-threatening allergic reaction. What thoughts and questions come to mind as you hear this scenario?

12. Of the following factors, which **two** would you rank as most important to your decision about whether to participate in a clinical trial to study an experimental treatment?
    a. Common side effects (such as nausea or diarrhea)
    b. Rare but serious side effects (such as bleeding or life-threatening allergic reaction)
    c. How the treatment might improve my health
    d. How the trial might affect my current treatment plan
    e. Requirements of the trial (such as blood tests or hospital stays)
    f. Length of the trial

13. If you / your loved one had the opportunity to participate in a clinical trial to study an experimental treatment, which of the following best describes your thoughts on participating?
    a. **Yes:** I would want to know more, 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 willing to consider participating or not

Appendix 4: Incorporating Patient Input into a Benefit-Risk Assessment Framework for Sickle Cell Disease

Introduction

Over the past several years, FDA has developed an enhanced structured approach to benefit-risk assessment in regulatory decision-making for human drugs and biologics.[4] The Benefit-Risk Assessment Framework involves assessing five key decision factors: *Analysis of Condition*, *Current Treatment Options*, *Benefit*, *Risk*, and *Risk Management*. When completed for a particular product, the Framework provides a succinct summary of each decision factor and explains FDA's rationale for its regulatory decision.

In the Framework, the *Analysis of Condition* and *Current Treatment Options* rows summarize and assess the severity of the condition and therapies available to treat the condition. The assessment provides an important context for drug regulatory decision-making, including valuable information for weighing the specific benefits and risks of a particular medical product under review.

The input provided by patients and patient representatives through the Sickle Cell Disease Patient-Focused Drug Development meeting and docket comments will inform our understanding of the *Analysis of Condition* and *Current Treatment Options* for this disease.

The information in the top two rows of the sample framework for sickle cell disease below draws from various sources, including the input summarized in this report. This sample framework contains the kind of information that we anticipate could be included in a framework completed for a drug under review for sickle cell disease. This information is likely to be added to or changed over time based on a further understanding of the condition or changes in the treatment armamentarium.

[4] Commitments in the fifth authorization of the Prescription Drug User Fee Act (PDUFA V) include further development and implementation of the Framework into FDA's review process. Section 905 of the FDA Safety and Innovation Act also requires FDA to implement a structured benefit-risk framework in the new drug approval process. For more information on FDA's benefit-risk efforts, refer to http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm326192.htm.

Sample Sickle Cell Disease Benefit-Risk Assessment Framework

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	– Sickle cell disease is a group of hereditary disorders characterized by the distorted crescent or "sickle" shape of red blood cells. – The disorder is estimated to affect 100,000 Americans, and occurs in about 1 in 12 African-Americans. – Symptoms and can affect every body system. Complications include pain crises, acute chest syndrome, fatigue, difficulty concentrating, and stroke. Over time, blood vessel damage and reduced blood and oxygen flow can result in organ, tissue and bone damage, pulmonary hypertension, vision and hearing loss, and many other effects. – The persistence and severity of symptoms and frequent hospitalizations can have extensive negative effects on a patient's quality of life and ability to function in society. Patients report high levels of social isolation, stigmatization, and difficulty accessing appropriate healthcare. – *See the Voice of the Patient report for a more detailed narrative.*	Sickle cell disease is a rare, serious disorder that disproportionately affects African-Americans. The disease causes debilitating pain and physical impairment, and takes a significant emotional and social toll on patients' quality of life.
Current Treatment Options	– Therapies to prevent complications of sickle cell disease include: • Hydroxyurea, an FDA-approved treatment to increase production of fetal hemoglobin and reduce the occurrence of sickling-related complications. It is effective for many but not all patients, and side effects include nausea, loss of appetite, hair loss, and kidney or liver complications. • Chronic blood transfusions and exchanges, which are effective in raising normal red blood cell levels and reducing sickle cell complications. Treatment occurs in a hospital setting and requires intravenous access. Side effects include iron overload, alloimmunization, and injection site reactions. • Bone marrow or stem cell marrow transplantation, which can be curative but are associated with significant risks that often limit its use only for patients with significant complications. This treatment is also limited by the availability of appropriate donors. – Many therapies are used to manage disease complications. • Pain crises are often treated in a hospital setting. Prescription and over-the-counter pain relievers are also used for acute and chronic pain. • Penicillin and immunizations are frequently used, especially in children, to prevent infection. • Some patients rely on a restricted diet, supplements and herbal remedies, as well as non-drug therapies such as heat, massage, and relaxation techniques to manage their disease. – *See the Voice of the Patient report for a more detailed narrative.*	Current treatments are effective in reducing the number and severity of sickle cell disease complications. However, their efficacy varies from patient to patient, and significant treatment burden and side effects and can limit benefits or preclude use of treatment. The disease remains suboptimally managed in a significant portion of the population. Thus, there is a continued need for effective and tolerable treatment options for patients to improve daily functioning and reduce long-term complications.

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