

# **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

## **Hemophilia A, Hemophilia B, von Willebrand Disease and Other Heritable Bleeding Disorders**

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Center for Biologics Evaluation and Research (CBER)  
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## **Introduction**

On September 22, 2014, FDA held a public meeting to hear perspectives from patients with heritable bleeding disorders (hereafter called “bleeding disorders”), their caregivers, and other patient representatives. The meeting enabled discussion of the impact of bleeding disorders on patients’ daily lives, as well as discussions of currently available therapies, and patient considerations on drug development. 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 patient perspectives on their medical condition and on available therapies. Under this initiative, FDA is holding a minimum of 20 public meetings over the course of 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 bleeding disorders**

Heritable bleeding disorders are a diverse group of diseases, some of which involve lifelong defects in the clotting mechanism of blood. The most frequently occurring bleeding disorders include von Willebrand Disease (VWD), Hemophilia A, and Hemophilia B. Less frequent, yet also serious, heritable bleeding disorders include deficiencies of factors V, VII, XIII, fibrinogen,  $\alpha_2$ -antiplasmin, and platelet disorders such as Gray platelet syndrome.

VWD, caused by a deficiency of von Willebrand factor, is the most common inherited bleeding disorder, estimated to occur in one in 100 to 1,000 people, with equal occurrence among men and women. Hemophilia A, caused by a low level of factor VIII, is the second most common inherited bleeding disorder, affecting one in 5,000 males. Because Hemophilia A has an X-linked inheritance pattern, almost all patients are male. Similarly, Hemophilia B, caused by a deficiency of factor IX, has an X-linked inheritance pattern, with almost all patients being male; but Hemophilia B is less frequent than Hemophilia A, affecting one in 30,000 males. The less frequent bleeding disorders, mentioned in the paragraph above, occur with a frequency of one in several hundred thousand to over one million individuals.

Symptoms of heritable bleeding disorders may include frequent nose bleeds; prolonged and heavy menstrual bleeding; prolonged bleeding from cuts, trauma, dental extractions, and surgical procedures; as well as bleeding into internal organs, muscles, and joints. Intracranial hemorrhage is a particularly serious and life-threatening manifestation. Spontaneous bleeding may also occur without any obvious cause.

Current therapies depend on the type of bleeding disorder and the severity of bleeds, and may include platelet transfusions, fresh frozen plasma, cryoprecipitate, specific factor concentrates such as factor VIII or factor IX, and desmopressin. Supportive treatments, which may include hormone replacement therapies and pain medications, serve to manage symptoms rather than to alter the course or treat the underlying cause of the disease. New treatments include recombinant products designed to be longer lasting or less immunogenic than their native counterparts, and investigational gene therapy products are being studied as a possible cures for the hemophilia A and B.

## Meeting overview

During this meeting, FDA had the opportunity to hear directly from patients and patient caretakers about their experience with bleeding disorders and their treatment. Approximately 50 patients with bleeding disorders and their representatives actively participated either in-person or through the live webcast. Others in attendance included representatives from FDA, other federal agencies and the regulated industry, healthcare professionals, and patient organizations. According to participant responses (Appendix 3, Q 3), most patients, participating in person or via the webcast, had hemophilia A, followed in decreasing numbers by patients with hemophilia B, VWD, and a few patients with other factor deficiencies and platelet disorders. Given this distribution of participants, public comments and responses to questions reflected primarily the experiences of the hemophilia population, and secondarily, those of patients with VWD. Approximately half of the polling participants were between the ages of 17 and 49 years old. Notably, most participants appeared to be highly connected through social media, and research and support foundations, and were very familiar with drug development and regulatory processes.

Meeting discussions 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 inherited bleeding disorders. The questions for discussion (Appendix 1) were published in a Federal Register Notice (79FR 38909) 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. 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 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 information on the demographic makeup of participants, as well as the number of participants who 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<sup>1</sup>, which was open until November 28, 2014. Five comments were submitted: two from patient organizations, one from industry, and two from individuals. The comments received via the public docket have been incorporated into this summary.

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<sup>1</sup> 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](http://www.regulations.gov).

More information on the meeting, including the archived webcast and transcript (<https://collaboration.fda.gov/p5t5195ltou/?launcher=false&fcsContent=true&pbMode=normal>), is available on the meeting webpage: (<http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/WorkshopsMeetingsConferences/ucm401758.htm>)

## **Report overview and key themes**

This report summarizes the input provided by patients and patient representatives at the meeting. 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 bleeding disorders, health effects and impacts, and treatment experiences, reflect those of participants or docket commenters. This report is not meant to be representative of the views and experiences of the entire bleeding disorder patient population or any specific group of individuals or entities. There may be symptoms, impacts, or treatment experiences that are not mentioned in this report.

The input that FDA received from this meeting highlights the diversity of bleeding disorders, the range of disabilities and comorbidities that accompany the disorders, and the challenges that patients and caregivers face in dealing with these diseases, while striving to lead a normal life. Several key themes emerged from their input:

- Participants with hemophilia spoke about their ongoing struggle with pain and joint deterioration, and the accompanying diseases of aging such as arthritis and gout, which exacerbate their conditions. They described their limited mobility, easy bruising, and unpredictable bleeding into joints, soft tissue, muscles, and the brain. Participants, including those with bleeding disorders other than hemophilia, discussed the challenges of decreased school attendance, constrained social interactions, disrupted family life, and limitations in career choices. Participants bravely described their experiences with stress, anxiety, and depression that can often accompany their disease. Caregivers of patients, especially of young children, also told about becoming stressed, anxious, and depressed, given the weight of their on-going responsibility of caring for the patient, recognizing when a bleed is occurring, and treating a sometimes reluctant child.
- Participants stressed that the formation of inhibitors to factor VIII, and, to a lesser extent, factor IX, is the biggest challenge to effective therapy faced by patients with hemophilia A or B. Participants commented that bypassing and tolerizing medications to reduce or eliminate the effect of inhibitors are not always effective, are difficult to dose, and are expensive to use. In addition, they commented that bypassing medications can cause thrombosis. Participants emphasized the need to obtain more information about the cause of inhibitors and their association with a given product. They also expressed a strong desire to have a greater variety of therapeutic products for inhibitors, either to prevent inhibitor formation or to more safely and effectively manage them.
- Throughout the discussion, many participants described how hemophilia and other bleeding disorders can pose social and cultural challenges. They emphasized the need for treatments that allow patients to pursue activities such as sports and social activities. In

addition, participants stressed that quality of life endpoints should be included in the design of clinical trials. Participants shared that more attention should be paid to the social, psychological and financial impact of these diseases, and that the aim of treatment should not be just to survive but to achieve a high quality of life.

- Many participants shared the importance of building awareness and education about bleeding disorders and their treatments, specifically among physicians (especially those in emergency rooms) and pharmacists. One participant noted that not receiving immediate infusion of replacement factor in an emergency room can lead to debilitating and potentially life-threatening complications. Another told of having received treatment for hemophilia A, rather than for his hemophilia B, which had serious consequences. Participants felt that physicians should listen more, show respect to, and have trust in a knowledgeable patient about the status of his or her disease.
- Several participants commented that bleeding disorders in women are often under-recognized and under-treated. Some told about their difficulty in convincing a physician that they had a bleeding disorder in the first place, and then difficulty in receiving the correct diagnosis and treatment.
- Participants acknowledged that significant advancements in treatment have occurred over time, allowing patients to become more independent and to have more control over their lives. Nevertheless, participants expressed their desire for safer, better, and more innovative ways to treat bleeding disorders. Many participants indicated that options for treatment are not ideal, and are often accompanied by discomfort or risk. The discomfort of frequent venous infusions, the destruction of muscle tissue in the course of joint replacement or repair, and the potential for infection when implanted ports and catheters are used, particularly in small children, were cited as concerns by meeting participants. Several commented that pain is often undertreated and that opiates to treat pain pose a risk of addiction, or withdrawal symptoms, and can leave the patient with the social stigma of being called a “drug addict.”

Participants shared that the ideal treatment would be a cure, through gene therapy or a transplant, with no accompanying side effects and no need for continuing maintenance of therapy. Barring that, participants want safe, effective, potent, inexpensive, very long acting, and easy to administer products.

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

The first topic of discussion at the meeting focused on patients’ disease symptoms. In particular, FDA asked participants to discuss the symptoms and complications of their bleeding disorder and the resulting impact that these health effects exert on their daily lives. Four panelists provided comments to start the dialogue. They included a mother with mild hemophilia A, who has an 11-year-old son with severe hemophilia A and a FVIII inhibitor; a mother with mild hemophilia A and a son with hemophilia and an inhibitor; a man with severe hemophilia B; and a man with severe hemophilia A. These participants described the daily challenges they and their children face with their respective conditions. They also shared the significant fears, frustrations,

and stresses that they and/or their children experience because of their conditions. 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.

## **Perspectives on symptoms**

### *Joint Damage and Pain*

When queried on the impact of their disease symptoms, two thirds of responding participants (Appendix 3, question 7) cited joint damage and/or pain as having the most significant impact on their or their loved one's daily life. One participant told of having "six joint replacements – both knees, both elbows, one ankle, and one hip." Another described having "both... ankles fused, surgery on my elbows, and am facing the prospect of a shoulder replacement because of the chronic joint disease."

Participants also described very small "micro" bleeds that can occur without the usual signs of pain or swelling. One participant described experiencing no known trauma to his shoulder, but an x-ray showed extensive joint damage.

Several participants commented on the pain that frequently accompanies bleeding into the joints. As one mother said, "one of the most difficult symptoms to deal with is the joint pain during bleeding episodes. When my four-year-old son has bleeding into his knees or ankles, he is unable to walk. It is always a challenge to watch..." Another participant commented that, "just from sitting with my legs crossed for too long, I got an awful bleed in my ankle and I couldn't walk for like two weeks." Many participants expressed a high level of tolerance to pain, which they attribute to their chronic experience with pain. One participant stated, "I think we develop a threshold and a tolerance for pain very early in life, and we don't quite appreciate what normal is without pain...as a result pain is really vastly under-recognized within the community, and pain is vastly undertreated."

### *Bleeding into Muscles and Soft Tissues*

The effects of easy bruising and bleeding were vividly described by one participant "I was on an airplane and the seatbelt was a little tight around my waist and there was some turbulence. I ended up bleeding, you know, into my abdominal area." Another participant described kidney bleeds as being the "most serious bleeds."

### *Bleeding in the Head*

Participants described situations where bleeding into the brain was not adequately recognized and controlled. One participant shared that "two personal friends who have adult children now that, due to spontaneous cerebral bleeds or brain bleeds, are now deficient in their adulthood; ...bleeds that may start small generally have the opportunity to become quite a larger scale...impacting the mental capacity of our people." Another participant noted that micro bleeds in his head were difficult to diagnose: "I have a lot of micro bleeds in my head...I've had

blood clots, subdural hematomas. Spent months and months in the hospital, almost died...so micro bleeding is a big thing.”

### *Heavy Menstrual and Postpartum Bleeding*

Participants who are symptomatic carriers of hemophilia and have low levels of factor VIII shared their experiences with severe postpartum bleeding. As an example, one participant said “as [a person with] mild hemophilia, I bled for nine months postpartum and was told that was normal. And of course, was anemic and was taking iron.”

Participants with bleeding disorders other than hemophilia described their symptoms. One with VWD spoke about her experience “I did not have many symptoms until I was 15. I had severe menstrual hemorrhage. I passed out, my hemoglobin was four, and factor was not enough to control the bleeding...a big symptom has been breakthrough bleeding and not being able to stop the bleeding when it needs to be stopped...many times when I’ve had a G.I. bleed, I’ve also had a severe menstrual bleeding...”

One participant with afibrinogenemia shared that her first menstrual period “lasted 8 days and was extremely heavy and the doctor who was helping me through that said that that was a normal experience.” Another participant with factor V deficiency “experienced some significant bleeding during and after [her son’s] birth”, and explained that having a diagnosis “provided a huge explanation for years of prolonged, excessive menstrual bleeding, for all the bruises and the hematomas of unknown origin.”

### *Anxiety/Depression/Stress*

Anxiety and depression were cited by responding participants (Appendix 3, question 7) as the second symptom having the most serious impact on their daily lives. As one participant stated, “it’s important just to sort of talk about the anxiety issues and how depression impacts people with bleeding disorders. Sometimes I think it’s important to understand that disability is not just a medical condition...but it’s sort of sets social and cultural barriers to the full participation in social life.”

A number of caregivers described the stress of recognizing a bleed in children. One mother recounted that “the kids, when they’re younger, they get cranky and they stop using the joint. That’s the first time I recognized my son had an ankle bleed. He would, instead of walking, he would crawl.” Another told about her four-year-old that “when it’s first starting, he kind of tries to hide it at first because he knows he’s going to get his port accessed...he’ll usually start with a hint of a limp, and will try to hide that and will go find something to do and sit down somewhere to try to hide that.” On a similar note, a mother stated “my son had a head bleed when he was 16 months old. I missed the symptom that would have told me he was having it a week earlier, and not led to such bad things had I known.”



### *Disease Symptoms Exacerbated by Aging*

Participants spoke about how, with new and better therapies, they are now living longer than ever before, and are now beginning to experience the diseases of aging that exacerbate the pre-existing conditions brought on by their bleeding disorders. As one participant explained, “as we get older, we start having these other ‘old man’ diseases that come along with hemophilia and it is kind of tricky. Because if you have gout and you have a bleed in the same joint, the bleed doesn’t respond to factor because it is actually gout and the gout irritates, you know it’s a mess...and as we age, we’re going to [have] more and more challenges with heart disease and diabetes and all of those kind of things that come with age.”

Another participant described his concerns regarding hemophilia and aging - “there are some problems that we never expected to have because we weren’t supposed to live this long... [For example] ... obesity we know is a bigger problem in our community than in the general population [because of joint damage leading to a sedentary life]. Many of us have been on heart therapies through the HIV drugs, and cardiovascular disease in patients aging with hemophilia is not well understood. And so interventions to manage cardiovascular disease, so many of the typical interventions are contraindicated with the hemophilia...I worry about it because there’s a long history of cardiovascular disease in my family.”

Participants discussed other symptomatic comorbidities associated with aging including the pain of neuropathy that has worsened bleeding pain, longer recovery times, and the need to infuse more coagulation factor products more frequently.

### **Perspectives on the overall impact of bleeding disorders on daily life**

#### *Stress (also see page 8)*

Participants described the stress caused by the unpredictability of the disease. As one participant explained, “There’s going to be a bleed on a holiday. There’s going to be bleeds at 5 o’clock on Friday night. There’s going to be bleeds around back to school. I mean, there’s almost some that you just know are coming. I think it’s a high part of stress.” Participants commented that stress can exacerbate bleeding. As one said, “I also find just the arthritic pain creates stress...not being able to walk and having that pain throughout the morning or until my ankles loosen up. That, in and of itself, creates some anxiety that I’m going to bleed worse and I usually end up doing just that. So I think that...is part of the same cascade.” Said another, “I find if I get all stressed out, I start to bleed a bit more in the neck, because the neck muscles get all tight and tense.”

#### *Career Choices*

A number of meeting participants discussed the limitations that bleeding disorders have put on the availability of jobs and career choices. One participant described how some people think that he is a drug addict because he takes methadone to treat his pain. He was disqualified from becoming a commercial driver because of being on methadone. An engineer recounted how “it’s frustrating to know that I could unstuck a bolt and not hurt myself if I could just get a longer

wrench to fit. Working under a car is out because I can't reach overhead. With my replaced knees, kneeling is out. Pretty much all I have left is telling other people what to do. It's fun in its own right, but not as satisfying as doing it myself."

### *Residence*

Several participants explained the impact of treatments on their daily lives, including making decisions on their place of residence to be close to a treatment center. One participant said "I was forced to make decisions on where I was going to locate and have my career because I knew with the complications – not only the hemophilia, but the HIV and the viral infections – that I needed to be near a major medical center. I grew up in rural Kansas. I grew up four hours from my treatment center and was forced to spend a lot of time in a car in a very painful situation waiting to get to the nearest access for treatment."

### *Sports*

A few participants commented on the balance they or their loved ones have had to strike between participating in sports versus the risk of bleeding. As one participant shared, "...within the last 20 years, I gave up riding a bike. It was just too painful. It was too difficult. And even recently, one of my favorite activities, swimming, is very problematic because of the problems in my shoulder. I do maintain a relatively active life, but the sports and the activities, in which I can engage, despite being on prophylaxis, are still limited because of my disease." Another said "my son is unable to participate in many physical activities due to hemophilia. He is unable to participate in sports due to the risk of injury. Although he is young and is not ready for many sports, this is difficult because he has an older brother who does not have hemophilia...it is difficult to explain to a young boy why he cannot play a sport."

### *School*

Several participants told about the difficulty they or their loved ones have in attending school. One mother recounted "[My son] misses an average of 20 school days per year. During the past year, he missed an entire trimester due to the shoulder bleed and the resulting dependency on pain medications...even after he had recovered enough to attend school, he had to remain home one day a week for us to retain eligibility for the homebound teacher." Another mother spoke about her young son at school "those kids rally around him and take care of him, but we've had some bullying instances where kids have thrown stuff at him in his wheelchair."

### *Family Life*

A common theme expressed by many meeting participants was the effect that a bleeding disorder can have on the daily life of a patient's family as well as that of a patient, especially when the patient is a child. One mother described her child's treatment that involved "couch rest", necessitating that during his bleeds he not participate in any activity himself. She stated that "he rests on the couch and watches TV. We even have to carry him to the bathroom. During these events, we usually have to cancel any family activities that were previously planned...because of the multiple treatments, I, myself, often have to miss work, as I'm his primary caregiver."

Participants spoke about the restrictions that they have not only in playing some sports or attending school, but also in doing routine tasks such as opening a jar or using a wrench. One participant explained that his “number one goal right now in life is to be a great father to my daughters, but -- especially with twins, sometimes I have both of them at the same time -- now I’m getting more and more elbow bleeds and shoulder bleeds just by carrying my daughters. So it does sadden me to think that I might be restricted in being the best father I can be and not being able to play catch or whatever other activities I wish I could do with them.”

### *Social Life*

Many participants described how hemophilia affects their interactions with others. As one participant shared “Sometimes I think it’s important to understand the disability is not just a medical condition...but it...sets social and cultural barriers to the full participation in social life, whether that be the pressure of fully participating in a sort of masculine world, and especially coming from a predominantly male-affected community, the issues begin to be even more compounded.” Participants talked about the stigma associated with the disease. One participant said that “if you complain about pain you might be considered a wuss or a sissy; there is a stigma associated with complaining about pain.” Another told about being condemned for parking in a handicap zone because he was viewed by others as being normal, despite his joint pain.

One participant talked about the concern he feels for people without a good support system. “People may not go to get the help they need because they’re afraid of the stigma that comes along with it. And then they’ll self-medicate or self-treat that pain or depression or anxiety.”

## **Topic 2: Patient Perspectives on Current Approaches to Treatments**

The second main topic of discussion focused on patients’ experiences with therapies used to treat their or their loved ones’ condition. Six panelists provided comments to start the dialogue. They included a woman with VWD; a mother with a factor V deficiency, who has a son with severe hemophilia B and a mild factor V deficiency; a mother of a son who has severe hemophilia A and an inhibitor; two participants with severe hemophilia A; and one with hemophilia B. Panelists shared their and their children’s experiences with a variety of treatment regimens, including prescription medications and lifestyle changes.

The following is a summary of the treatment perspectives 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:

- There exists a need for products which will prevent inhibitors, reduce joint damage and pain, be easier to administer, remain effective for a longer time, or provide a cure.
- Physicians and pharmacists should become better educated about bleeding disorders and be more attentive to a given patient’s needs and level of knowledge.
- Many participants are willing to join clinical trials that offer additional therapeutic options, but not at the risk of diminishing the effectiveness of their current treatment.

Much of the discussion in this part of the meeting involved participants' concerns about receiving or giving the appropriate treatment at the right time and in the right amount.

## **Perspectives on current treatment for conditions or symptoms**

### *General*

One participant described how he transitioned from fresh frozen plasma and whole blood to clotting factor concentrates. “As a child, I was expected to live into my early 30’s, and I think for many of us, we are still stuck in that definition of normal. Normal is surviving a normal life that everybody else has. And to me, normal is so much more than just a life expectancy. My goal isn’t to survive, but my goal is to actually have a high quality of life....we’ve really moved from that generation of treating the disease to the opportunity now to treat the individual, and.... about what are those life goals, those aspirations, and what are the things the individual wants.”

Similarly, a participant with afibrinogenemia expressed her appreciation for the improvement in therapeutic options: she could only be treated with fresh frozen plasma or cryoprecipitate “in the early days” but now takes a fibrinogen concentrate, which she finds effective and easier to infuse.

The fact that concentrate therapeutics are not currently available for some bleeding disorders was highlighted by one participant with a deficiency of factor V: “for me fresh frozen plasma is really only used as a treatment in case of trauma or surgery, and it’s administered via an IV in a hospital setting, so I’m limited. There is no day-to-day treatment available for factor V...”

### *Factor Replacement Therapy*

The overwhelming majority of responding participants (Appendix 3, question 9) identified factor replacement therapy as their primary treatment regimen. Several participants expressed gratitude for the impact that these treatments have had on their lives, and recounted experiences that they have had as these products have improved over time.

Several older participants said that gaining the ability for home infusion, in itself, was the greatest advance that they had experienced because it gave them more control over their lives. “[Current improvements] pale next to the change from hospital-based administration to self-infusion.”

Similarly, one patient appreciated the fact that a longer acting factor VIII product allowed him to reduce the number of infusions he needed from 3 to 4 times per week to twice per week, which gave him greater flexibility in his life.

A few participants with hemophilia described how the introduction of prophylactic therapy improved their lives. One participant with severe hemophilia reported that over the years, he changed from on-demand therapy, sometimes not infusing for weeks at a time (“I would either ignore bleeds or try to hide the bleeds from my parents, which I think was pretty common.”), to

prophylactic therapy and infusing every day. A mother reported that the introduction of prophylaxis therapy has reduced joint damage, which she saw by comparing the joint damage in her older son who did not have prophylaxis treatment to that of her younger son who did.

### *Risks and Concerns About Current Treatment Options*

Participants discussed how treatment options for bleeding disorders can have their own hazards, side effects, and unintended consequences. For example, one participant reported that to repair his shoulder joint, surgeons had to cut through his shoulder muscles, which left him with a loss of strength in his arms. Another participant described that although catheters and implanted ports are sometimes needed for venous access in the course of immune tolerance induction, particularly in young children, the use of these devices has led to infections in her son, and has restricted his physical activity.

### *Inhibitors*

Many participants stressed that inhibitors to factor VIII and factor IX are currently the major complications of therapy with concentrates, that the presence of an inhibitor can have a devastating effect on a patient and his family, and that current therapies leave much to be desired. One participant with mild hemophilia who developed an inhibitor after receiving a large amount of factor VIII for a wisdom tooth extraction stated: “I went through everything, from neuropathy on my left-hand side, to joint damage, to forming a clot, to frequent infusions.” Now the participant receives both a clotting factor and an anticoagulant.

Several participants spoke about their difficulty and the expense of treating an inhibitor with current therapies. One mother stated “I’m concerned that the inhibitor will not completely go away and that we will continue daily treatments. I’m concerned because of the fluctuation of the inhibitor and the ability for the factor VIII to be effective. If the inhibitor increases again, he will be at risk for more bleeds, which will eventually lead to joint damage.”

### *Bypassing Agents*

Several participants discussed the challenges and limitations that they had in using bypassing agents to control bleeding. One participant observed that she found factor VIII bypassing agents to have very short half-lives, they need to be given often, and require multiple doses to stop a bleed. She noted that no laboratory tests are available to titrate dosing of FVIII bypassing agents to ensure an effective treatment outcome. She further noted the potential for thrombotic complications associated with these therapies.

### *Dosing of Therapy*

Participants described the struggles of finding the correct dosage of clotting factor or bypassing agent. One participant noted that failing to treat a bleed aggressively, because of concern about overdosing, could lead to suboptimal therapy, which in the case of intracranial bleeding, could have dire consequences. Over-treating could result in clot formation and equally dire consequences. One caregiver shared that her son almost died from a blood clot after using a

bypassing agent and “spent three months in intensive care growing new veins.” She told about the difficulties in controlling kidney bleeding which is “the hardest to control because, again, you’re trying to treat but you don’t want to clot....we’re having this constant balancing between trying to treat a bleed and trying not to clot.”

### *Immune Tolerance Therapy (ITT)*

Similar to experiences shared by participants using bypassing agents, several participants described how the therapeutic effect of ITT could be unpredictable and expensive. One caregiver shared on behalf of her 18 month old son, “he started on a daily factor treatment of factor VIII in an attempt to tolerize the inhibitor. He has been on that treatment for over three years and has not tolerized at this time. There are periods of time when the factor VIII seems to help and work well, during which time he has no bleeding episodes. However, [recently] he has experienced many bleeds...I’m concerned that the inhibitor will not completely go away and that we will continue daily treatments.” Participants mentioned the difficulties of receiving ITT through catheters and ports, as noted previously in this report.

### *Pain Management*

Many participants expressed frustration that pain is vastly undertreated and not effectively controlled with current products. One mother shared, on behalf of her 11 year old son, “Chronic and acute pain management has also been a significant challenge...repeated joint bleeds into [my son’s] left ankle have miraculously caused very little visible damage, but he currently complains of soreness there and in other areas of his body. He recently said ‘Mommy, my body is like that of an old man’s. I’m just sore all the time.’”

Another mother described that for her son “most of our hospitalizations over the last three, four years have not been because of the bleed; it’s been because of the pain. And ultimately, treatment of the pain has snowballed such that the side effects from the drugs, pain drugs, and vomiting and low heart rate and sedation often become more of a problem [than] the bleed itself...we are at the stage now where he doesn’t want pain medication.”

Several participants expressed fear that opiates to treat pain may lead to addiction. One caregiver commented “the suffering my 10-year-old son had to go through during the withdrawals for such powerful, yet mildly effective, drugs was something I would never wish on my worst enemy.”

### *Recognition and Treatment of Bleeding Disorders*

Many participants expressed concern that physicians and pharmacists, particularly those in emergency room settings, often did not recognize, understand, or appropriately treat bleeding disorders. One participant reported being asked by a physician in an emergency room, who clearly did not understand that hemophilia is an inherited bleeding disorder, “And how long have you had hemophilia?” Another participant told about the death of his brother who was not treated quickly enough. “[In the emergency room (ER)] it’s the stroke mentality. We have a

golden hour. We CT [scan] first. It's either a clot or a bleed. We treat accordingly. With hemophiliacs, that's not the issue. Infuse stat. [i.e. immediately]. We need to get that to ERs."

A participant with Hemophilia B described an episode in an emergency room where he had "to have a carpal tunnel release because it was such a significant bleed. Turns out that the medication I was prescribed was for factor VIII deficiency, not factor IX...it was kind of a significant bleeding episode that was just a mistake from the pharmacist dispensing."

Many meeting participants voiced concern and frustration that physicians may not be aware of a patient's own understanding of the severity of their disease. One participant told about having a bleed in his elbow, but because the treating physician could not see the bleed the physician was convinced that it was arthritis.

Throughout the meeting, many participants described the challenge that women with bleeding disorders face in convincing physicians that they have a bleeding disorder. One symptomatic carrier of hemophilia recounted "it was a fight for me to get the physicians to listen. [They] say you are a female and you're a carrier of hemophilia. You can't be affected by hemophilia. And so it really took a lot of lab work for them to see it [low factor VIII activity] and actually believe it because of the fact that they needed that lab level to actually qualify that for their thought processes." Another participant commented that even after she had been identified as a carrier of hemophilia, and was experiencing severe postpartum bleeding, she had difficulty in convincing a physician, who simply refused to believe that she had a deficiency of factor VIII, and that she needed to be treated with factor concentrates.

#### *Other Treatment Considerations*

A participant with VWD described trying many different medications to obtain a combination that works. She found that DDAVP worked sometimes but then she had a life-threatening side reaction.

Several participants expressed concern that the product they now take and are happy with, will be removed from the market by manufacturers to be replaced by longer acting products. They said that they might be forced to take a new long-acting product because it might be cheaper than their current product; and some feared that they might experience allergic reactions with these new products for which there is little long-term clinical experience. One participant questioned whether a new product would be covered by insurance.

A number of participants shared their concern about the expense of bypassing agents and their fear that insurance companies might not be willing to continue to pay for them. One mother shared that the cost of purchasing bypassing agents for her son amounted to millions of dollars per year.

One participant commented that because hepatitis C is a major issue in the hemophilia community, medication to treat it should be available and be covered by insurance.

## *Non-Drug Therapies*

Meeting participants described treatments that they use in addition to, or other than taking factor concentrates or bypassing agents. Their comments included:

- Exercising to the extent that one can is important. Although exercise can lead to bleeding, strength and balance are improved which can help to avoid future bleeding. A participant commented that changing his lifestyle to obtain more physical therapy was very important in improving his condition.
- Use of ice and aqua therapy can be helpful.
- Synovectomy is an alternative to factor in treating target joint bleeds that are not responsive to bypassing agents.

## **Perspectives on an ideal treatment**

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

- Many participants stressed the need for better ways to prevent and treat the formation of inhibitors and to improve surveillance to monitor their occurrence. As one participant commented, “The World Federation of Hemophilia has identified inhibitor development as the number one safety issue associated with hemophilia treatment... The morbidity and mortality of those with inhibitors are greater and the quality of life is less. We need better products, and not just different versions of the same treatments. We need more effective ways to induce tolerance. And stronger warnings and more detailed product labeling are needed for consumers to make informed treatment decisions.” Another participant added that an ideal inhibitor bypass product would be one that has a low volume and can be infused infrequently.
- A few participants expressed their concern that some factor products might have molecular properties that are more conducive to inhibitor formation in non-Caucasian populations. As one participant said “I think personally there needs to be more research into whether products themselves can be matched more ideally to specific patients. I think we need to know why these inhibitors are developing at such an alarming rate, one third of patients.” Another participant said “I think we can look at non-Caucasian communities being highly more impacted by these inhibitors and I think when you look at new technologies and new treatments, you might start thinking about individualized medicine and how potentially the cell lines<sup>2</sup> [sic] that are being used to create these products sort of perpetuate a kind of institutionalized racism when we’re talking about inhibitor development in our community.”

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<sup>2</sup>Hypothetically “the higher prevalence of inhibitors in black patients may be due in part to the greater degree of population-level variation that exists in their factor VIII amino acid sequence and the resultant increased probability of a mismatch with replacement factor VIII proteins” Howard, et. al. N Engl J Med 2009;360:1618-27



- Many participants commented on their desire for treatments that can enhance their, or their loved ones' daily quality of life. As one participant said "...my desire for normal is to lead a comparable life to someone who is not affected with a bleeding disorder.... We need to shift our clinical focus and to build the outcome around outcomes that are important to patients, not just relevant clinical endpoints, so that I don't have to make decisions about my life goals related to the disease." Another participant said "my goal isn't to survive, but my goal is to actually have a high quality of life. And as we think about the dimensions that mean a normal quality of life, it is going to be very much individualized.... The new criteria should be...more than factor levels in terms of treating to clinical numbers... it should be about what's required for me as an individual to have a normal work and career life."
- A number of participants commented that a patient should be treated according to the patient's symptoms rather than just on the level of factor when assigning the patient to a severe, mild, or moderate category.
- Many participants expressed similar perspectives that, outside of a cure, which would be ideal, a better treatment should be longer acting, have zero risk of inhibitor formation, could be taken subcutaneously or orally, and would be safe.
- One participant commented that industry has little incentive to find a cure because of the profitability of current products, and that the federal government should invest in a gene therapy cure for hemophilia.
- A number of participants with bleeding disorders other than hemophilia expressed their desire for products to treat rarer bleeding disorders like deficiencies of factors V, X, or XIII. One participant with afibrinogenemia commented that she preferred a non-blood based product due to her fear of an infection from plasma derived products.
- One participant spoke of his desire for a simple way to measure the level of factor in his blood at home and to know when it reaches a certain trough level. Another would like a mobile device to detect and monitor factor levels.
- A number of participants noted the need for better treatment options for replacing joints.

### **Perspectives on participating in clinical trials**

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.

In response to a polling question (Appendix 3, Q14), almost a third of participants (or their loved ones) have participated in some type of clinical trial studying experimental treatments for bleeding disorders, and several others indicated that they would have liked to participate but could not for various reasons. In response to a follow-up question, about three quarters of

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 considerations that affect their decision-making. The following examples illustrate the perspectives shared.

- Throughout the meeting, participants across the spectrum of heritable bleeding disorders, expressed an urgent need for more and faster advancements in drug development, including clinical trials for experimental therapies. Participants at the meeting commented on the kinds of clinical trials that should be conducted. Among their recommendations: more research is needed on the relationship between genotyping and inhibitor formation, and between inhibitor formation and specific products; and there should be mandatory phase 4 tracking of inhibitor formation for assessing the relationship between product and inhibitor formation.
- A few meeting participants indicated a willingness to take part in a trial only if it were for a demonstrably “better option – a curative gene therapy or a treatment with a longer half-life.” Similarly, one patient would sign up for a cure or a trial for a subcutaneous therapy.
- A representative from the advocacy organization Hemophilia Federation of America said that patients need to have access to a variety of treatments and be engaged in a transparent and open dialogue about any data collected on the impact of treatments.
- Participants commented on the challenges of entry into clinical trials, including one participant who has severe symptoms but not a corresponding low level of factor. He said that although he wanted to take part in a clinical trial, he was excluded because the maximum factor level for inclusion into the trial was too low.

### **Perspectives on risk and uncertainty in heritable bleeding disorders drug development**

- Many participants cited the need to have a clear understanding of the risk and benefits of participating in a clinical trial. Said one “As a parent, if I was looking at putting my child in this study, my biggest question would be... If a bleed did happen, how would we be able to get that under control? What would be the impact of his actual hemophilic disease state and the damage that could be done to the joints if they went untreated?” Another participant said he would want to be certain that a bleed could be controlled and shared that he would be willing to tolerate the side effects.
- A few participants commented on the risks and benefits of having previously untreated patients (PUPS) involved in clinical trials. One said that PUPS should be included in clinical trials since they are most at risk for inhibitor development. However, another said that he would have no concern as an adult, but would be concerned about a child’s participation, particularly with regard to the potential of inhibitor formation.
- One participant shared that before he would enter into a clinical trial, he would have to consider the science behind the clinical trial; the potential of what the product would be

offering to the hemophilia community; and whether or not the efficacy of his current product would be affected.

- A number of participants cited the need for hemophilia treatment centers to be involved in disseminating information about clinical trials. They said that hemophilia treatment centers should have access to new advances, with a full understanding of their risks and benefits, and that they should provide a more thorough discussion of the pros and cons of taking a given product. One participant said that he would want himself and his hemophilia treatment center to have all options open so that he could choose with knowledge of potential benefits and risks. An older participant said he would volunteer to be in a risky trial for the sake of future generations.

## **Summary of Comments Submitted to the Docket**

The FDA received a total of five submissions to the docket. One comment, from an advocacy organization, Change, stressed the need to include previously untreated patients in clinical trials, and to monitor the formation of inhibitors in post-licensure follow-up studies of coagulation products.

One docket commenter noted that caregivers should have less fear about causing addiction in children who are receiving pain medications because new drugs are available to treat childhood addiction.

The National Hemophilia Foundation provided results from an online survey, posed to individuals (and their caregivers) with hemophilias A and B, VWD, platelet disorders, and rare factor deficiencies, that asked questions similar to those presented at the FDA meeting. The findings of the survey were consistent with those identified during the public meeting with regard to patients' concerns and the need for development of new therapies.

Novo Nordisk described a study they conducted, named Hemophilia Experiences, Results and Opportunities (HERO), on the characteristics and perceptions of patients with hemophilia and their caregivers. The study identified "pain and functional impairment as well as the impact on work and relationships as current issues for our young adults (ages 18-30) highlighting that more ought to be done beyond just encouraging prophylaxis for children with hemophilia. The interdependency of treatment-related variables, including access to factor and comprehensive care, bleed and visit frequency, treatment regimen, and perceived disease control also highlights the need to capture patient-based information in studies like HERO to better understand and interpret the impact of psychosocial issues on patients and caregivers."

One commenter is seeking help for her daughter who has VWD and a connective tissue disorder. She is looking for more treatment options that could address her daughter's frequent infections and difficulty in healing,

The submissions from the National Hemophilia Foundation, Novo Nordisk, and Change can be viewed at <http://www.regulations.gov/#!docketDetail;D=FDA-2014-N-0851>.

## Conclusion

This Patient-Focused Drug Development meeting gave government agencies, health care providers, and the drug development industry a rare opportunity to hear directly from patients and their advocates about their past and current struggles with bleeding disorders, gaps in the management of their diseases, and what they would like to see in the future to allow them to lead normal, fulfilling lives. We are grateful to those who contributed to this meeting, who took the time and effort to present their views, and who had the courage to talk about their personal, and often, painful experiences.

It is clear that although there have been great advances in the development of products to treat bleeding disorders, more needs to be done not only to develop new therapies and to reduce or eliminate their adverse side effects, but to address broader economic, social, and educational barriers that still remain. The FDA shares the patient community's commitment and desire to further the development of safe and effective drug therapies for patients with hemophilia A, hemophilia B, VWD, and other heritable bleeding disorders.

The perspectives shared at the Patient-Focused Drug Development meeting are highly relevant to FDA regulatory activities. Input from the patient focused workshop has strengthened our understanding of challenges faced by patients with bleeding disorders, and it serves to inform FDA's interactions with manufacturers on the development of new therapies. FDA considers these patient and caregiver perspectives when deciding on measures of therapeutic effectiveness, including patient reported outcomes, and when evaluating the benefits versus the risks of new drugs. Testimony, on the challenge of living with inhibitors, underscored the importance of advancing our knowledge of the immunogenicity of therapeutic coagulation proteins. Consistent with this priority, FDA, in partnership with the National Heart, Lung and Blood Institute, National Institutes of Health, the National Hemophilia Foundation, and the Plasma Protein Therapeutics Association, held a public workshop in September 2015: New Methods to Predict the Immunogenicity of Therapeutic Coagulation Proteins.

These are some examples of the lasting impact of the Patient-Focused Drug Development meeting. The FDA thanks the patient community for its participation and for its valuable contributions to the understanding of heritable bleeding disorders, and the effect of these diseases on patients and their families.

## Appendix 1: Meeting Agenda and Discussion Questions



# Patient-Focused Drug Development for Hemophilia A, Hemophilia B, von Willebrand Disease and other Heritable Bleeding Disorders: Public Meeting

September 22, 2014



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8:00 – 9:00 a.m.	<b>Registration</b>
9:00 – 9:05 a.m.	<b>Welcome</b>  Donna Lipscomb <i>Office of Communication, Outreach and Development (OCOD)</i> <i>Center for Biologics Evaluation and Research (CBER), FDA</i>
9:05 – 9:10 am	<b>Opening Remarks</b>  Ginette Michaud, M.D. <i>Deputy Director, Office of Blood Research and Review (OBRR)</i> <i>CBER, FDA</i>
9:10 – 9:20 a.m.	<b>Overview of FDA’s Patient-Focused Drug Development Initiative</b>  Theresa Mullin, Ph.D. <i>Director, Office of Strategic Programs</i> <i>Center for Drug Evaluation and Research (CDER), FDA</i>
9:20 – 9:40 a.m.	<b>Background on Heritable Bleeding Disorders</b>  Stephanie O. Omokaro, M.D. <i>Medical Officer, DHCR, OBRR, CBER</i>
9:40 – 10:00 a.m.	<b>Overview of Discussion Format</b>  Donna Lipscomb <i>OCOD, CBER, FDA</i>
10:00 – 10:30 am	<b>Topic 1: The effects of your bleeding disorder that matter most to you</b> <b>Panel Discussion on Topic I</b> A panel of patients and caregivers will provide comments followed by a large-group facilitated discussion with participants in the audience.
10:30 – 11:45 a.m.	<b>Large-Group Facilitated Discussion: Topic 1</b> Patients and patient representatives in the audience will be invited to contribute to the discussion.
11:45 – 12:45 p.m.	<b>Lunch</b>

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12:45 – 12:50 p.m.	<b>Afternoon Welcome</b> Donna Lipscomb <i>OCOD, CBER, FDA</i>
12:50 – 1:20 p.m.	<b>Topic 2: Patients’ perspectives on current approaches to treatments</b> <b>Panel Discussion on Topic 2</b> A panel of patients and caregivers will provide comments followed by a large-group facilitated discussion with participants in the audience.
1:20 – 2:15 p.m.	<b>Large-Group Facilitated Discussion: Topic 2</b> Patients and patient representatives in the audience will be invited to contribute to the discussion.
2:15 – 2:30 pm	<b>Patient perspectives on participating in a clinical trial to study experimental treatments</b> Patients and patient representatives in the audiences will be invited to contribute to a discussion on Topic 2 Question 3.
2:30 – 3:00 p.m.	<b>Open Public Comment</b>
3:00 – 3:15 p.m.	<b>Closing Remarks</b> Ginette Michaud, M.D. <i>Deputy Director, OBRR, CBER, FDA</i>

## **Appendix 2: FDA and Patient Panel Participants**

### **FDA Panelists**

Donna Lipscomb	Office of Communication, Outreach and Development (OCOD), Center for Biologics Evaluation and Research (CBER) Food and Drug Administration
Ginette Michaud	Office of Blood Research and Review (OBRR), CBER
Stephanie Omokaro	Division of Hematology Clinical Research (DHCR), OBRR, CBER
Jonathan Goldsmith	Office of New Drugs (OND), Center for Drugs Evaluation and Research (CDER)
Changting Haudenschild	Division of Clinical Evaluation and Pharmacology/Toxicology (DCEPT), Office of Cellular, Tissue and Gene Therapies (OCTGT), CBER
Menfo Imoisili	Office of Special Medical Programs (OSMP) Office of Orphan Products Development (OOPD), Office of the Commissioner (OC)
Diane Maloney	Office of the Director (OD), CBER
Paul Mintz	DHCR, OBRR, CBER
Nicole Verdun	Division of Hematology Products (DHP), Office of Hematology and Oncology Products (OHOP), OND, CDER

### **Patient Panelists**

#### **Topic 1**

Daniel Bond  
Mark Skinner  
Amanda Heisey  
Sonji Wilkes

#### **Topic 2**

Josephine Droney  
Donald Goldman  
Kimberly Haugstad  
Debbie Porter  
Benjamin Shuldiner  
Mark Zatyryka

## Appendix 3: Meeting Polling Questions

The following questions were posed to in-person and web meeting participants at various points throughout the September 22, Patient Focused Drug Development for Hemophilia A, Hemophilia B, von Willebrand Disease and Other Heritable Bleeding Disorders Patient-Focused Drug Development meeting. Participation in the polling questions was voluntary. The results were used as a discussion aid only and should not be considered scientific data.

### **Patient Focused Drug Development for Hemophilia A, Hemophilia B, von Willebrand Disease and Other Heritable Bleeding Disorders Patient-Focused Drug Development:**

#### **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
  - c. International
2. Which of the following best describes you?
  - a. I have a heritable bleeding disorder
  - b. I am a family member or caretaker of someone with a heritable bleeding disorder
  - c. I work for a patient support or advocacy organization
3. Have you/your loved one been diagnosed with any of the following bleeding disorders?
  - a. von Willebrand disease
  - b. hemophilia A
  - c. Other factor deficiencies
  - d. Platelet dysfunction
4. What is your/your loved one's age?
  - a. 0 – 12
  - b. 13 – 16
  - c. 17 – 49
  - d. 50 – 65
  - e. older than 65
5. Are you/is your loved one:
  - a. male
  - b. female
6. In the past year, how often have you/your loved one had to go to the hospital or the emergency room because of your bleeding disorder?
  - a. none in the past year
  - b. 1 – 2 times
  - c. 3 – 5 times
  - d. 6 – 10 times



- e. more than 10 times
7. Which of the following symptoms currently has the most significant impact on you/your loved one's life?
- a. joint damage and/or pain
  - b. heavy menstrual bleeding
  - c. bleeding in the muscles and soft tissues
  - d. bleeding in the head
  - e. anxiety/depression
8. How many times the past year did you/your loved one experience a bleed?
- a. 0 – 4 times
  - b. 5 – 11 times
  - c. 12 – 23 times
  - d. 24 times or more
9. Name one therapy used to manage your/your loved one's bleeding disorder, in the past year?
- a. Factor replacement therapies
  - b. Platelet transfusion
  - c. DDAVP (desmopressin)
  - d. Clot stabilizing medications
  - e. Hormone replacement therapy
10. If you/your loved one are being treated with factor replacement therapy, what is the current treatment regimen?
- a. On demand therapy
  - b. Routine prophylaxis
  - c. Both
11. If you/your loved one are being treated with routine prophylaxis, how often do you receive replacement therapy?
- a. 2-3 times per week
  - b. once weekly
  - c. once every 2 weeks
  - d. more than three times per week
12. Which of the following best describes how you/your loved one feel about your current treatment regimen?
- a. I am satisfied with my current treatment regimen and do not want to change it.
  - b. I am satisfied with my current treatment regimen, but am willing to consider new options.
  - c. I am not satisfied with my current regimen
13. Have you /your loved one ever participated in any type of clinical trial studying experimental treatments for heritable bleeding disorders?
- a. Yes

- b. No
  - c. I'm not sure
14. Would you/your loved one participate in the hypothetical clinical trial described today?
- 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
15. Which of the following factors 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) or length of trial