

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

Pulmonary Arterial Hypertension

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Center for Drug Evaluation and Research (CDER)
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Introduction

On May 13, 2014, FDA held a public meeting to hear perspectives from patients living with pulmonary arterial hypertension (PAH, also referred to as PH by some meeting participants) about their disease, its impact on their daily life, and currently 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 and 2017, 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 pulmonary arterial hypertension

Pulmonary arterial hypertension is a rare and progressive disorder characterized by abnormally high blood pressure (hypertension) in the pulmonary artery. In patients with PAH, the average pulmonary arterial pressure is 25 mm Hg or greater at rest (compared with 15 mm Hg in patients without PAH). The condition is characterized by a range of symptoms, including shortness of breath, tiredness, chest pain, dizziness, fatigue, and swelling of the legs and ankles. Symptoms can develop slowly early on, and range in severity among patients. There are three types of PAH, 1) Idiopathic PAH, 2) Familial PAH, and 3) Associated PAH, in which PAH is associated with another disease or condition.

There is no cure for PAH; however, there are several treatment options that aim to reduce symptoms, improve the quality of life, and slow disease progression. These drugs include endothelin receptor antagonists (ERAs), phosphodiesterase-5 inhibitors (PDE 5 Inhibitors), and prostacyclins. Other prescription drugs (used off-label) include anticoagulants, calcium channel blockers, diuretics, digoxin and non-drug therapies, such as inhaled oxygen, and lifestyle modifications, such as diet and exercise, are also used to manage symptoms.

Meeting overview

This meeting provided FDA the opportunity to hear directly from patients, patient caregivers, and patient representatives about their experiences with PAH and its treatments. Discussion focused on two key topics: (1) disease symptoms and daily impacts that matter most to patients and (2) patients' perspectives on current approaches to treating PAH. The questions for discussion (*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. The discussion was led by an FDA facilitator, and a panel of FDA staff (*Appendix 2*) asked follow-up questions. Participants who joined the meeting via live webcast were able to submit comments throughout the discussion, and their comments are incorporated into this summary. In-person and web participants were periodically invited to respond to polling questions (*Appendix 3*), which provided a sense of the demographic makeup of participants, as well as of how many participants shared a particular perspective on a given topic.

Approximately 60 pulmonary arterial hypertension patients or patient representatives attended the meeting in-person, and approximately 25 patients or patient representatives provided input through the live webcast and polling questions. According to their responses to the polling questions, in-person and web participants represented a range of patients, with a higher proportion of women participating. The majority of in-person patients were between ages 31 and 70, and most had been diagnosed with PAH in the last 10 years. Although participants at this meeting may not fully represent the PAH patient population, FDA believes that the input received reflects a range of experiences with the known PAH symptoms and treatments.

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 July 14, 2014. Seventeen comments were submitted to the public docket.

More information, including the archived webcast and meeting transcript, is available on the meeting website: <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm379694.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. To the extent possible, the terms used in this report to describe specific PAH symptoms, impacts and treatment experiences reflect the words used by in-person attendees, web participants, or docket commenters. The report is not meant to be representative in any way of the views and experiences of any specific group of individuals or entities. There may be symptoms, impacts, treatments, or other aspects of the disease that are not included in the report.

The input from the meeting and docket comments underscores the chronic and debilitating effect that PAH has on patients' lives and the challenges patients face in finding effective and tolerable therapies to help manage their condition. Several key themes emerged from this meeting:

- PAH is a progressive, devastating disease. Participants described living with daily shortness of breath, persistent fatigue, and chest pain, in addition to a range of other debilitating symptoms. Many shared their fears of symptoms continuing to worsen over time.
- PAH affects all aspects of patients' lives. Participants described the dramatic change from their active and vibrant lives before diagnosis. Many participants noted that the significant decline in health caused them or their loved ones to limit or completely stop participating in activities and tasks that they once enjoyed or were able to do.
- Nearly all participants described using a combination therapy in addition to non-drug therapies in their treatment approach. Many participants were able to identify whether a treatment was or was not effective, and described making difficult decisions on benefits versus adverse effects of treatments and switching to alternate treatment, if necessary.

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.

- Participants emphasized the continued need for medications that are effective, have convenient dosing schedules, and are easy and safe to administer. They also emphasized the need for further research and education on PAH, including for pediatric and geriatric patients.

The remainder of this reports details the experiences and views shared by meeting participants and docket commenters. The patient input generated through this Patient-Focused Drug Development meeting and public docket strengthens FDA’s understanding of the burden of PAH on patients and the therapies currently used to treat PAH and its symptoms. FDA staff will carefully consider this input as it fulfills its role in the drug development process, including advising sponsors on their drug development programs and assessing the benefit-risk for products under review for marketing approval (see Appendix 4). 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 PAH patients, such as with regards to shortness of breath or fatigue. It could also point to the potential need for development and qualification of new outcome measures in clinical trials.

Topic 1: The Effects of Pulmonary Arterial Hypertension That Matter Most to Patients

The first discussion topic focused on patients’ experiences with their PAH symptoms and the resulting effects on their daily lives. FDA was particularly interested in hearing about specific activities that patients can no longer do at all, or as fully as they would like, because of their condition.

Five panelists with PAH provided comments to start the dialogue, including four women and one man. Two of the panelists were more recently diagnosed and two others spoke of experiencing symptoms for several years prior to a formal diagnosis. The panelists described the depth of challenges they face with a range of PAH symptoms, and the impact that their symptoms have on their ability to perform daily activities. They also described the significant frustration and fear they have experienced because of their condition. 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. Several participants shared experiences of being misdiagnosed with other conditions, such as asthma, emphysema, and epilepsy.

Perspectives on most significant symptoms

In a polling question (Appendix 3, Q7), participants were asked to identify up to three symptoms that have the greatest impact on daily life. Shortness of breath and fatigue received the highest number of responses, followed by dizziness and swelling of the legs and ankles. Responding web participants reported similar results to those in person. The facilitated discussion provided a look into how symptoms manifest and how they have changed over time. The range of symptoms discussed by in-person and web participants is described in more detail below.

Shortness of breath

The most frequently discussed symptom by in-person and web participants was shortness of breath. Participants described their lives after PAH as a “new normal” in which they constantly monitored or avoided physical activities that triggered breathing difficulties. As one panelist described, having to schedule his life around shortness of breath “can bring my daily activities to a screeching halt.”

The degree to which participants described shortness of breath varied from person to person. For one participant, “breathing is different, slightly harder;” another compared shortness of breath to “running a marathon.”

Participants identified a range of triggers to shortness of breath, shown below. Many participants agreed that any type of exertion resulted in bouts of shortness of breath. Examples of triggers of shortness of breath mentioned by participants are listed below:

- Standing
- Bending
- Twisting
- Walking
- Weather conditions
- Climbing (hills or stairs)
- Completing household chores
- Picking up heavy loads
- Playing with children
- Talking

The following examples illustrate the range of triggers and experiences shared by meeting participants:

- “I wasn't able to walk the 50 feet from my car to the elevator at my building or even up the stairs from my living room to my bedroom. I feel short of breath and lightheaded just walking around the house or trying to do normal household chores.”
- “I lost my voice right after I was diagnosed, and I really had to strain to get even a whisper out. It would wear me out to have a short conversation, and talking made my shortness of breath worse.”
- “If I keep to my own slow pace I can walk a good distance without really feeling a shortness of breath. But almost immediately with bending or twisting, loading and unloading the dishwasher, doing laundry, anything that takes lateral movement I feel shortness of breath extremely quickly.”
- “When my children were babies...Picking them up, cooking for them, cleaning after them, these things would make me so short of breath I'd get palpitations and I would pass out.”

Several in-person and web participants commented on the significant role that weather has on their ability to breathe. High heat or intense cold were particularly problematic for participants, and breathing difficulties were compounded by wind or humidity. One person described being unable to “leave the house in any weather condition other than the ideal.” Other participants noted that the difference in breathing was noticeable outdoors regardless of weather conditions. One participant commented, “I can walk about one mile on a treadmill indoors without any problem. I can barely walk a block outside. It is a lot more difficult to walk... outside, no matter whether it is warm or cold.”

Fatigue

Nearly one-third of in-person participants and over three-fourths of web participants identified fatigue as one of the most significant symptoms of PAH impacting their daily life. Fatigue was described by participants in unique ways, including: exhaustion due to physical exertion, a constant feeling of tiredness or lack of energy, and a “sudden crash” that occurs without warning. The following examples illustrate the experiences shared in the discussion of fatigue by in-person and web participants:

- “Nowadays napping is not a luxury; it is a necessity. And if I don't get a nap for whatever reason... I have zero energy for anything other than sitting.”
- “The fatigue started with me just being groggier in the morning but it progressed to me falling asleep at my desk at work. I've fallen asleep at a stop light. And I have fallen asleep in the driveway waiting for the garage to lift up.”
- “The erratic-ness of the fatigue is hard to plan for. It arrives unexpectedly and [is] not a ‘cause and effect.’”
- “A busy day today might mean a day of recovery tomorrow to recover my energy level. My energy is less than half of what it was five years ago.”

One phone participant shared various manifestations of fatigue, stating: “your body becomes fatigued... your muscles themselves get tired... your brain becomes fatigued.” This comment appeared to resonate with many of the in-person meeting participants.

Participants also agreed that there was a significant and stark difference between routine tiredness (caused by exertion) and PAH-triggered tiredness. One participant commented, “With PH you can sit in the chair for five hours and do nothing, and get up and feel like you have ran back and forth in this room for thirty minutes.” Another participant noted, “... you get tired doing anything that requires oxygen, and that is like 90 - 95% of everything that you do.”

Other symptoms

In addition to shortness of breath and fatigue, participants described a number of other symptoms that have a significant impact on their daily lives:

- Many participants described **orthostatic intolerance** and symptoms related to drops in blood pressure, including dizziness, lightheadedness and fainting. As one participant explained, “My heart would flutter or I would get lightheaded just walking the aisles of the grocery store. I would have to stop for frequent rests because I would pass out if I didn't.”
- Several participants described **chest pain** as another significant health effect. Chest pain was described as a persistent feeling of “heaviness” or “tightness” that makes it difficult to breathe. One participant described feeling “like a wall is against my chest.” Another participant described difficulty sleeping, sharing, “if I laid down, I would feel pressure on my chest as if I couldn't breathe.” Some participants noted that they experience chest pain along with shortness of breath (from exertion), and/or fatigue. One participant shared that she experienced “tightness and heaviness” with both shortness of breath and chest pain.
- Participants described their experiences with **heart palpitations**. Several participants described feeling their heart “racing” or “fluttering.” Other participants shared similar experiences with irregular heartbeats and “sharp pangs” in the chest which sometimes occur spontaneously as well. A few participants noted that climbing stairs or inclines often resulted in heart palpitations. One participant noted, “walking up the stairs by myself causes my oxygen to drop significantly and my heart to race. “

- **Prolonged, frequent respiratory infections and complications** were identified and described as severe episodes that took weeks or months to recover from. Several participants described respiratory symptoms progressing from a simple cough or chest cold into debilitating bouts of bronchitis and pneumonia.
- **Cognitive effects** were frequently described in terms of difficulty concentrating, memory problems and “PH brain.” One phone participant described PH brain as an inability to think clearly “because there simply isn’t as much oxygen in my brain consistently.” Another web participant shared, “Some days I feel foggy, forgetful, and can't think clearly.”
- **Other symptoms** mentioned included leg cramps, bloating in the belly, swelling (such as in the legs or ankles), fluid retention, anxiety, depression, and voice changes.
- A range of **comorbid conditions** were identified during the meeting, including lupus, mixed connective tissue disorder, congenital heart defect, and heart attack.

Overall impact of PAH on daily life

Both in-person and web participants described in rich detail the impact that their condition has on their daily life, including:

- **Participating in household activities.** Participants described the significant impact of PAH symptoms on the ability to perform routine household activities. As one participant explained, “daily activities such as cooking, washing dishes, family errands are often exhausting.” Another participant noted, “I must add time to my daily tasks, as lapses in concentration make it much harder to complete certain jobs than I once was able to.” Other participants focused on their inability to participate in family activities, such as playing with their children, or having the “energy or ability actually to keep up.”
- **The ability to perform at work.** Participants shared that their symptoms, particularly shortness of breath and fatigue, had significant impacts on their ability to perform at their job or maintain a full-time work schedule. One panelist commented, “I couldn't catch my breath to give a presentation or even to keep up with my peers walking down the hallway. It was very embarrassing and I would tell people that I was having a bad asthma day.”
- **Feeling a loss of independence or purpose.** Several participants described the limitations they have encountered as they have adapted to living with PAH. One participant commented, “I would love to become a productive member of society again. Going back to work, not having to rely on family and friends to support me; being able to work a 40 hour work week...would be wonderful.”
- **Other impacts** mentioned by participants include the debilitating effects PAH symptoms have on relationships with their spouses and children, embarrassment at experiencing symptoms while out in public, fear of being alone and without help during severe bouts of symptoms, and the impacts of treatments and side effects on their well-being.

Topic 2: Patient Perspectives on Treatments for PAH

The second discussion topic focused on patients' experiences with therapies used to treat PAH. Five female panelists living with PAH provided comments to start the dialogue, one of whom was also a representative of a patient organization. Four of the panelists were middle aged adults, and one panel member was under the age of thirty. All had been living with PAH for the last six to eight years. Following the panel comments, another participant in the audience was asked to share the experiences of her eight year old son living with PAH, which provided a pediatric perspective.

In the large-group facilitated discussion that followed, nearly all patients and patient representatives indicated by a show of hands that their experiences (or those of loved ones) were reflected in the panelists' comments. Participants described a complex process of trial and error, and transition between various medications to find an effective treatment regimen (including drug and non-drug therapies) to fit their specific needs. The facilitated discussion included prescription and over-the-counter drug therapies as well as a variety of non-drug and alternative treatments. Participants' perspectives on the benefits and downsides of these therapies are summarized below. This section ends with participants' perspectives on ideal treatments for PAH as well as other aspects of PAH healthcare that they believe are important to consider.

Prescriptions and over-the-counter drugs

According to a polling question (Appendix 3, Q7), the majority of in-person and web participants reported taking or having taken endothelin receptor antagonists (ERAs), phosphodiesterase type 5 (PDE5) inhibitors, or prostacyclins. Supplemental oxygen was also identified by participants as an important component of therapy. Nearly all participants commented on using a combination of two or more of these treatments. Prescription drug therapies were described as having widely varying degrees of effectiveness, and many participants noted limited or decreased benefit over time. Further, participants described that even if their treatment is effective, they could not sustain that treatment because they were unable to tolerate the side effects of the drug. Their experiences with specific drugs are summarized below.

Combination Prescription Treatment Regimens

Participants described their experiences with combination prescription treatment regimens in some detail. Based on participant input, there did not appear to be a clear pattern of use regarding which class of drug was prescribed first, or how subsequent treatments were added. Rather, participants shared experiences that highlighted a trial-and-error process to determine an effective individualized treatment regimen. As one participant noted, "I wanted to try one treatment at a time so that I could gauge which might be helping me and how I might be impacted by side effects." Another participant commented, "I am so grateful that there were other drugs we could turn to, we didn't have just one choice."

The majority of both in-person and web participants identified that they have experiences taking ERAs, such as Tracleer (bosentan) and Letairis (ambrisentan), and PDE5 Inhibitors, such as Revatio (sildenafil) and Adcirca (tadalafil). About half of in-person and web participants shared that they have taken or are taking a prostacyclin, such as Flolan (epoprostenol sodium) or Remodulin (treprostinil), as part of their treatment regimen.

The comments below reflect participants' experiences with combination therapy that they found to be effective for them, and, importantly, how they determined that the drug or combination therapy was effective:

- “My improvements after a few months were significant. I could tell it in my oxygen levels. I could tell it in my energy and my stamina” (experience with Tracleer/Revatio).
- “[My son’s] PH is stable and has shown no sign of progression since then” (experience with Revatio/Inhaled Trepostinil/Flolan).
- “I have been able to take back small parts of my life. My walk distances have improved... I can manage a very light workout, a walk around town with my wife” (experience with Tracleer/Adcirca/Tyvaso).
- “Today I feel like I function just about as well as I did prior to diagnosis which is a huge improvement for me” (experience with Letairis/Revatio/Tyvaso).
- “This combination of drugs is working really well for me... I can do multiple errands in one day. I rarely need to take a morning or afternoon nap. I have much more energy and stamina to accomplish daily tasks as well as enjoy some leisure time and low key activities” (experience with Tracleer/Revatio/Ventavis).

FDA asked participants if they were able to identify specific medications within their combination therapies that were most effective in treating PAH symptoms. Based on their responses, it appears that many patients may find it difficult to tease out which specific medication provided the most relief; however, a few participants indicated they were able to do so, as illustrated below:

- One web participant shared that upon starting intravenous Remodulin, “I was able to walk much farther, and do much more than I ever had before... my life has changed significantly for the better with this medication. It has changed my life and made it livable again!” This comment resonated with several others in the meeting.
- One participant described her experience with Flolan, sharing “I feel it has saved my life.”
- One participant who used a combination of Letairis/Adcirca/Remodulin noted that her symptoms had improved so significantly that she decided to remove Adcirca from the treatment regimen (believing that Letairis and Remodulin were sufficient in treating her symptoms). Within two months of removing Adcirca, she experienced a change in her breathing and increased difficulty walking. The participant noted that she needed to add Adcirca back to her combination treatment again to achieve the previous level of symptom relief.

Other prescription therapies

In addition to the medications described above, many participants also stressed the importance of supplemental oxygen therapy in their treatment regimen. Several commented that they are on supplemental oxygen “24/7.” A few participants noted that they are taking or have taken Lasix (furosemide) to treat fluid retention; one participant noted frequent urination as a significant side effect of Lasix. Other therapies included warfarin, digoxin, Opsumit (approved for PAH WHO Group-1), Procardia, Klor-Con, Ventolin (albuterol sulfate), and imatinib.

Treatment Downsides

In many cases, participants acknowledged that treatments are effective but can be burdensome due to a range of issues, as described below.

- Participants described their most bothersome side effects from treatments, including dizziness, pain (for example: all-over body pain, jaw, leg and skin pain), mood swings, photosensitivity, fluid retention, nosebleeds, and gastrointestinal issues. For example, one participant commented on how calcium channel blockers resulted in excess swelling, stating, “My legs were probably 20 pounds heavier each side. I couldn't put any socks and shoes on and I didn't feel any benefit other than like a swollen mess.”
- Several participants commented on the downsides of intravenous (IV) medications. They commented on fears of site infections and how living with an IV line impacts daily activities. One participant described frequently waking up to “readjust my IV line so that it is not being pulled or tangled.” Another shared, “I hate the tube in my chest. I hate cleaning the site and changing the dressing...my line is always getting caught on something.”
- A few participants shared that carrying or transporting oxygen tanks can be very cumbersome when performing activities such as walking or traveling. Another noted that she experiences disrupted sleep, sharing, “it is just best not to turn over for fear that at some point my tubing will become a noose around my neck.”
- One participant noted the emotional burden of monthly pregnancy testing and counseling required by some PAH medications. She commented, “We do not want to have to relive every month the way this disease has taken one of life's most precious gifts of being able to have our own children. And yet we are forced to as if we could ever forget for a minute what this disease has done, not only to our lungs.”
- The effect of missing a dose of medication was mentioned. One patient noted, “Days when I miss my morning scheduled Tadalafil I feel sluggish by noon and notice breathing is different, slightly harder. Similarly, if I do not replace the Remodulin within that 24 hour shelf life I feel like a wall is against my chest, a slight tightening begins.”
- Access to medications was also identified as an issue. Some participants shared that many of their medications do not have automatic refills and are dispensed through specialty pharmacies. One participant shared, “I personally experience quite a few barriers to getting my medications in a timely fashion primarily due to issues with the order and delivery process.” This comment resonated with others who shared a similar perspective.

Perspectives on choosing or changing treatment

Participants were able to identify the effects they experienced as a result of adding, removing, or switching a medication as symptoms improved or worsened. Other changes to treatments included altering the dose or route of administration. While some participants shared that they are able to immediately determine whether a medication is or is not effective, others shared that they try a medication for three to four months before making changes. Several participants commented that drug regimens can be complex, inconvenient, and difficult to incorporate into daily life.

The range of experiences for altering medications throughout treatment is presented below.

Intolerable Side Effects

- “[On Flolan] it felt like every last piece of skin was constantly being pinched. The sharp pain never went away. I tried Veletri but couldn't finish the transition; the pain was ten times worse. [Later] I successfully transitioned from Flolan to Tyvaso. Within a week I was completely pain free. Breathing is better than ever and so are the test results.”
- “I felt dizzy and within four to five weeks, I could no longer think or read [on Ventavis]. So they put me on the Flolan at that time...within a week and half of being on Flolan my brain unwound as my cardiac output improved and that was a huge, huge life changer for me.”
- “I started with Revatio and then it was changed to Adcirca. Then we tried Tracleer because my pressures were not what they should be and that did not work for me because of the liver situation. So I am on Letairis now and that seems to be working fine for my body.”

Dosing

- “I made the decision to switch from Revatio to Adcirca because... mid-day dosing was getting missed. When you are trying to maintain an active daily schedule stopping to take an additional medication during the middle of the day just got forgotten.”
- “The prescribed dosage [for Ventavis] is six to nine treatments a day. When I first started these treatments...I was not awake for 12 hours a day to be able to accomplish that. The most I was ever able to do consistently was seven. I was never able to do eight or nine in one day. My current dose is five which is manageable.”
- “[My son] started his treatment with low doses of Revatio. Every month the dose was increased until he reached 20 milligrams three times a day. Reaching the proper dosage of 20 milligrams took months to achieve. However, the hard work paid off.”

Route of Drug Administration

- “The pain that I experienced [on subcutaneous Remodulin] was unbearable...it feels like a hot burning iron is on your skin continuously. So I opted to go the IV route and I've never looked back since.”
- “Tyvaso liberated me from the tube in my chest and the machine at my waist. I no longer feared the next site infection, the next line break, the next life and death crisis.”
- “I have been able to switch to...Veletri, which is a giant quality of life improvement to not have those ice packs on your hip and a frozen hip for years.”
- “I did go on a couple of oral medications but ... they made me so flushed and I just felt terrible with them. I even tried it one time coming off all IV medication and going with oral. And I went like for four months and I just couldn't breathe. So they had to put me back on IV treatment.”

Some participants, however, said that they chose not to change medications because they believed the benefits outweighed the negative effects. For example, one web participant commented on how her life has changed “significantly for the better” on Remodulin, although she mentioned a range of side effects, including jaw pain, leg pain, sensitivity to light, fluid retention, gastrointestinal issues, and IV site pain.

One participant, taking Flolan, shared a similar perspective. Another participant shared that in spite of the cumbersome maintenance required for the Ventavis nebulizer, she noticed a “big improvement” in her oxygen and stamina levels. Another participant shared that she experiences nosebleeds and mood swings on Tyvaso; however, “In spite of all the negative effects these drugs have I would have died without them.” Finally, one participant candidly commented that she is “too afraid to try something else for fear of it not working as good.”

Perspectives on non-drug therapies

In addition to their medical treatments, participants emphasized the importance of a holistic approach to managing PAH symptoms. As one participant commented, “fighting [PAH] is a mind, body, and soul approach.” A summary of these therapies is listed below.

- Some participants stressed the importance of dietary modifications to manage their PAH symptoms. This included avoiding or limiting sugar, sodium, and fatty foods. Several participants noted that a low sodium diet helped to minimize fluid retention. Other participants commented that they became organic vegetarians, maintain vegan diets, and/or take dietary supplements (such as vitamins and minerals).
- Some commented on relaxation and other emotional therapies, including yoga, meditation, and prayer. Others commented on physical therapies such as massage, acupuncture, and routine chiropractic visits. One participant noted relying on alternative medicine, including reiki therapy.
- Several participants noted that they incorporate exercise into their lifestyle, such as swimming and walking. Others noted that pacing and resting is an important part of lessening the impact of PAH symptoms. One participant commented that stopping to rest in the afternoon was critical, “or I have a difficult time making it through the rest of the day.” Participants noted that it helps to take frequent rests between activities, and to plan the day in increments.
- Other therapies mentioned included pulmonary rehabilitation and using a continuous positive airway pressure (CPAP) machine.

Perspectives on an ideal treatment for PAH

Many participants commented that an ideal treatment would be less invasive, have fewer side effects, and address the pervasive symptoms of PAH. A few participants also mentioned the importance of a holistic approach in the treatment of PAH, to include natural and alternative therapies.

FDA asked participants to share, by a show of hands, which symptom was most important to them in the search for treatments. The majority of in-person participants and a large number of web participants agreed that shortness of breath was the most significant symptom they hoped to address.

Several participants mentioned that an ideal treatment would bypass the need for IV administration and the use of other cumbersome apparatus. One participant shared that she wished for a treatment option (other than oral, IV, or subcutaneous) that would allow for “freedom and flexibility... without fear of infection,” such as a patch or an implantable pump. Others noted the need for smaller pumps which would allow for pain-free targeted therapy. Several participants also noted the need for improved oxygen delivery systems. One web participant shared that she wished for “lighter portable tanks and a longer battery life.”

Participants also shared that they hoped to have effective treatments with more convenient dosing schedules. For example, one participant shared that an ideal treatment would be, “A medication that is as effective as Ventavis but lasts longer so that the treatments only need to be done three or four times a day [and] is in an inhaler form instead of a nebulizer.” One web participant shared that an ideal treatment would not “interfere with daily life activities... such as not having to mix medications, stress during simple showers and sleep, change sites, or [stopping] everything to do a breathing treatment.”

Additionally, several issues were raised that participants strongly felt required further research and education. For example, one participant discussed that targeted, innovative therapy, such as the use of stem cells and genomic technology, would help to provide effective, personalized care. A few participants discussed the critical need to improve research on PAH therapy in pediatric and geriatric patients. A mother of a pediatric PAH patient shared, “Additional research and trials that will get our kids appropriate treatment options would be priceless.” Finally, one participant stressed the need for “full coordination and communication between all government agencies and medical participants to work together on a best treatment and possible cure.”

Comments on six-minute walk test

Several participants shared their experiences with monitoring their PAH symptoms using the six-minute walk test. FDA asked participants whether they routinely undergo the six-minute walk test and track progress; the majority of participants responded by a show of hands that they do. Several commented that their treatment therapies have increased the distance they are able to walk during the exam and that this is one way that they can identify whether their treatment therapies are effective or which symptoms were improving. FDA also asked participants whether it was shortness of breath or fatigue which most impacted how they perform on a six-minute walk test. The majority of responding participants shared that shortness of breath had a greater impact on the ability to walk faster during the six-minute walk test. A patient advocate who spoke during Open Public Comment suggested that the six-minute walk test does not truly reflect the impact of weather on PAH symptoms and the ability to walk.

Summary of Comments Submitted to the Public Docket

FDA received 17 comment submissions to the public docket that supplemented the Patient-Focused Drug Development meeting on PAH. The majority of comments were submitted by patients, and one comment was submitted by a caregiver. FDA also received one comment from the advocacy organization Pulmonary Hypertension Association, which submitted the results of a study that included patient perspectives on improved diagnostic criteria and treatment options for pediatric and adult patients. One comment was also submitted by an industry representative.²

In general, the docket comments reflected the input generated at the meeting and provided greater depth of explanation in some areas, including the progression of symptoms, the limitations on daily life, and the breadth of experiences with treatment options. The following is a brief summary of their comments, highlighting the areas of similarity and difference compared to the meeting input.

² Because this report centers on PAH symptoms, impacts, and patients’ treatment options, comments pertaining to these subject matters are the focus of this report. The comments to the docket covered a wide range of other important topics related to drug development for PAH, such as research topics, improving clinical trial designs and developing or improving outcome assessment tools to advance PAH therapies. Comments on these topics were also reviewed and considered by FDA.

Submitted comments on symptoms of PAH

Similar to what was heard during the public meeting, comments submitted to the public docket reemphasized the debilitating effect of PAH. Docket commenters identified 7 different types of symptoms of PAH, which were all discussed during the public meeting. These include:

- Shortness of Breath
- Chest Pain / Tightness
- Fatigue
- Balance Issues
- Anxiety / Depression
- Cardiovascular Issues
- Cognitive Issues

Several commenters reiterated the burden of shortness of breath. As one described, “no matter how much oxygen I am on, or how little activity I am completing at the time, it never feels like I can fully catch my breath.” Another commenter described the progressive worsening of her shortness of breath, sharing “I used to be able to climb 3 flights before... now I can feel the tightness in my chest after the second flight.” Commenters also shared that weather plays a significant role in the severity of their shortness of breath.

Several commenters also shared that chest pain and tightness were a “constant” and debilitating symptom of PAH. As one commenter noted, “If it's not a sharp pain, then it's a dull weighty thud. Most of the time, it is just a feeling of extreme weight on my upper torso.” Another shared, “sometimes you will feel like your own ribs are “stabbing you.”

Similar to what was heard during the meeting, commenters emphasized that constant and “excruciating” fatigue was a difficult symptom to manage, adding that even little exertions, such as lifting a cup of water, could be very tiring. As one commenter noted, “on my worst days, PH makes it hard to be a young, active mom and wife.”

Some commenters shared that they have experienced worsening of symptoms, while others noted that their symptoms have remained steady. One commenter said that her symptoms slowly progressed over the last 7 years of her diagnosis; another commenter shared that within 6 months of diagnosis, her symptoms have steadily progressed.

Submitted comments on the overall impact of PAH on daily life

The docket comments echoed the input received during the meeting related to the debilitating impact that PAH has on patients’ daily lives, and the significant social, emotional, and financial toll the disease has on patients and their families.

Most commenters shared that difficulty with physical activity due to PAH had the most impact on their lives. Commenters noted that walking within their home, doing routine household chores (such as vacuuming or laundry), and even light exercise could result in low oxygen levels, increased heart rate, shortness of breath, and extreme fatigue. Others noted that hobbies and interests were no longer pursued, such as travelling or continuing a cherished profession. One commenter noted that the exertion required to work an 8-hour shift made it difficult to continue working full time, resulting in financial concerns. This perspective was shared by other commenters also.

Many commented on the emotional impacts of living with PAH. Commenters shared feelings of fear, embarrassment, and frustration due to PAH symptoms. One commenter noted that chest pain “scares

you to death,” while another compared living with PAH to the ups and downs of a rollercoaster. One commenter shared frustration that plans are often cancelled last minute because of symptoms, impacting relationships with family and friends. Another commenter, who shared a similar perspective, noted that this made her feel like she has lost her independence. Finally, one commenter noted the stigma she feels, sharing that while she may not look sick, “PAH doesn’t mind if you look young or old.”

Submitted comments on current treatments for PAH

The submitted comments reflected the challenges of managing the many symptoms of PAH, and reflected experiences that were similar to those at the public meeting. Most combination therapies mentioned included an ERA, PDE5, and a prostacyclin, in addition to other drug and non-drug therapies. Other drug therapies mentioned included Lasix (furosemide), Klor-Con (potassium chloride), Opsumit, warfarin, nitric oxide gas, and spironolactone.

Similar to the experiences shared at the public meeting, commenters discussed the effectiveness of their overall treatment regimen. In some cases, commenters were able to provide examples on what specific medication was or was not effective. A sample of their experiences with treatments is provided below:

- “The medications I take to treat my PH have given me my life back. I drive my kids to practice, I cook dinner, I shop and meet friends for lunch, and do regular household chores.”
- “The medications, primarily Remodulin, changed my life within days. I measure this by things like better stamina, ability to enjoy a variety of activities, interest in going new places and doing new things, being less cautious about what I do on a daily basis.”
- “Adding Ventavis was very good because it helped to make my grocery shopping easier with less shortness of breath.”

Commenters reiterated the importance of supplemental oxygen as a critical part of therapy. Some commenters noted that they were on continuous oxygen, while others noted they only required oxygen during sleep or travel. One commenter shared that oxygen therapy was most effective, adding “it keeps me from feeling like I’m suffocating from the inside out.” However, others commented on the burden of transporting and traveling with oxygen tanks, which itself exacerbates exhaustion.

Docket commenters also reiterated the importance of non-drug therapies, including dietary modifications such as reducing/eliminating salt intake and eating a vegetarian or whole-foods diet. Other therapies included cardiopulmonary rehabilitation, frequent rest, and light exercise.

Downsides to Drug Therapies

Commenters also described the side effects of treatments. In some cases, commenters noted that treatment benefits outweighed troublesome negative effects. Others commented that side effects were too intolerable to continue treatment.

- “The side effects... for me are a little bothersome, but nothing I can't deal with; sore throat, cough, headache.”
- The mother of a deceased child shared, “It seemed that she was suffering more from the medication side effects than the PH itself.”

- Other side effects noted included vomiting, headaches, gastrointestinal issues, joint and jaw pain, fluid retention and fatigue. However, the majority of commenters shared that despite these downsides, their treatments were helping to manage their symptoms.
- Similar to what was heard during the meeting, several commenters described the downsides of inconvenient dosing schedules and routes of administration. One commenter described the multi-step process to prepare her medication, sharing, “At this point (with lots of practice) it takes about ½ hour.” She shared the difficulties of managing all of the supplies needed to administer the IV medication precisely and with the utmost care in order to avoid site infections.

Submitted comments on ideal treatments for PAH

Several perspectives were provided on ideal treatments for PAH. The majority of commenters shared the need for medications that were easier to administer or had more convenient dosing schedules. Commenters noted their desire for more oral medications rather than intravenous medications. A few commenters shared that taking a pill only a few times a day would allow for more freedom and mobility. One commenter identified the need for improved diagnostic procedures other than the six-minute walk test sharing, “If I had a bad night’s sleep, or wear the “wrong” shoes, or other actions unrelated to PAH, the walk number can be dramatically different.”

Others identified the need for increased education and awareness of PAH in the medical community (especially for pediatric patients), and the need for increasing patient perspectives on PAH into drug development.

Conclusion

The Patient-Focused Drug Development meeting on PAH provided the FDA an important opportunity to obtain patients’ in-depth point of view on the severity of PAH, its impact on daily life, and available treatment options. FDA recognizes that patients have a very unique ability to contribute to our understanding of the broader context of this disease, which is important to our role, and that of others, in the drug development process. We are grateful to all of the participants who so generously shared such personal stories, experiences, and perspectives. FDA shares the patient community’s commitment to furthering the development of safe and effective drug therapies for PAH.

PAH 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 truly admire the strength of the participants who demonstrated their resolve in the face of adversity presented by their PAH. This was perhaps best exemplified by one participant who shared during the meeting, “Life with PH is not easy and the current treatments are not perfect. But these treatments enable us to defy the odds with every breath we take. We are alive; we will live to see tomorrow; and tomorrow may hold a cure.”

Appendix 1: Meeting Agenda and Discussion Questions



Patient-Focused Drug Development Meeting Pulmonary Arterial Hypertension



12:00 – 1:00 pm	Registration
1:00 – 1:05 pm	Welcome Soujanya Giambone, MBA <i>Office of Strategic Programs (OSP), Center for Drug Evaluation and Research (CDER), FDA</i>
1:05 – 1:10 pm	Opening Remarks Ellis Unger, MD <i>Director, Office of Drug Evaluation I, CDER, FDA</i>
1:10 – 1:20 pm	Overview of FDA’s Patient-Focused Drug Development Initiative Theresa Mullin, PhD <i>Director, OSP, CDER, FDA</i>
1:20 – 1:30 pm	Background on Pulmonary Arterial Hypertension and Therapeutic Options Shari Targum, MD <i>Division of Cardiovascular and Renal Products (DCaRP), CDER, FDA</i>
1:30 – 1:40 pm	Overview of Discussion Format Soujanya Giambone, MBA <i>OSP, CDER, FDA</i>
1:40 – 2:10 pm	Panel #1 Comments on Topic 1 Topic 1: Disease symptoms and daily impacts that matter most to patients. A panel of patients and patient representatives will provide comments to start the discussion.
2:10 – 2:55 pm	Large-Group Facilitated Discussion on Topic 1 Patients and patient representatives in the audience are invited to add to the dialogue.
2:55 – 3:10 pm	Break
3:10 – 3:40 pm	Panel #2 Comments on Topic 2 Topic 2: Patient perspectives on current approaches to treating pulmonary arterial hypertension.
3:40 – 4:25 pm	Large-Group Facilitated Discussion: Topic 2
4:25 – 4:55 pm	Open Public Comment
4:55 – 5:00 pm	Closing Remarks Norman Stockbridge, MD, PhD <i>Director, DCaRP, CDER, FDA</i>

Discussion Questions

Topic 1: Disease symptoms and daily impacts that matter most to patients

- 1) Of all the symptoms that you experience because of your condition, which 1-3 symptoms have the most significant impact on your life? (Examples may include chest pain, shortness of breath, difficulty concentrating, etc.)
- 2) Are there specific activities that are important to you but that you cannot do at all or as fully as you would like because of your condition? (Examples of activities may include household chores, walking up the stairs, etc.)
 - a) How do your symptoms and their negative impacts affect your daily life on the best days?
On the worst days?
- 3) How has your condition and its symptoms changed over time?

Topic 2: Patient perspectives on current approaches to treating pulmonary arterial hypertension

- 1) What are you currently doing to help treat your condition or its symptoms? (Examples may include prescription medicines, over-the-counter products, and other therapies including non-drug therapies such as diet modification.)
 - a) How has your treatment regimen changed over time, and why?
 - b) How well does your current treatment regimen treat the most significant symptoms of your disease?
 - c) Have the medications for pulmonary arterial hypertension made a difference to you? If so, in what ways?
- 2) What are the most significant downsides to your current treatments, and how do they affect your daily life? (Examples of downsides may include bothersome side effects, going to the hospital for treatment, etc.)
- 3) Assuming there is no complete cure for your condition, what specific things would you look for in an ideal treatment for your condition?

Appendix 2: FDA and Patient Panel Participants

Patient Panel, Topic 1

- Kevin Paskawych – Patient
- Cynthia "Alex" Flipse – Patient
- Nicole Matthews – Patient
- Holly Tissue-Thompson – Patient
- Colleen Connor – Patient

Patient Panel, Topic 2

- Lucille Monko – Patient
- Colleen Brunetti – Patient
- Katie Tobias – Patient
- Stacey Gausling – Patient
- Tamera Pixler – Patient

FDA Panel

- Ellis Unger, Office of Drug Evaluation I, CDER
- Norman Stockbridge, Division of Cardiovascular and Renal Products (DCaRP), CDER
- Shari Targum, DCaRP, CDER
- Anne Pariser, Rare Diseases, Office of New Drugs, CDER
- James Bona, Office of Orphan Product Development, CDER
- Theresa Mullin, Office of Strategic Programs, CDER

Appendix 3: Meeting Polling Questions

The following questions were posed to in-person and web meeting participants at various points throughout the September 24, 2014, Pulmonary arterial hypertension Patient-Focused Drug Development meeting. Participation in the polling questions was voluntary. Their results were used as a discussion aid only and should now be considered scientific data.

Demographic Questions

1. Where do you live?
 - a. Within Washington, D.C. metropolitan area (including the Virginia and Maryland suburbs)
 - b. Outside of the Washington, D.C. metropolitan area

2. Have you ever been diagnosed as having pulmonary arterial hypertension?
 - a. Yes
 - b. No

3. Are you:
 - a. Male
 - b. Female

4. Age:
 - a. Younger than 10
 - b. 11 – 20
 - c. 21 – 30
 - d. 31 – 40
 - e. 41 – 50
 - f. 51 – 60
 - g. 61 or greater

5. What is the length of time since your diagnosis?
 - a. Less than 5 years ago
 - b. 5 years ago to 10 years ago
 - c. 10 years ago to 20 years ago
 - d. More than 20 years ago
 - e. I'm not sure

Question for Topic 1

6. Of all the symptoms you have experienced because of pulmonary arterial hypertension, which do you consider to have the most significant impact on your daily life? **Please choose up to three symptoms.**
 - a. Cataplexy
 - b. Daytime sleepiness
 - c. Hallucinations while waking up or falling asleep
 - d. Sleep paralysis
 - e. Difficulty sleeping

- f. Restless leg syndrome
- g. Activity while sleeping, such as sleepwalking
- h. Other symptoms not mentioned

Question for Topic 2

7. Have you ever used any of the following drug therapies to help reduce your symptoms of pulmonary arterial hypertension? (check all that apply)
- a. Modafinil, armodafinil, methylphenidate, amphetamine
 - b. Anti-depressants (off label use)
 - c. Xyrem (Sodium oxybate)
 - d. Other drug therapies not mentioned
 - e. I'm not sure
8. Besides your drug therapies, what therapies have you used to help reduce your symptoms of pulmonary arterial hypertension? (Check all that apply)
- a. Naps
 - b. Dietary modifications
 - c. Exercise
 - d. Counseling and support groups
 - e. Other therapies not mentioned
 - f. I'm not using any additional therapies

Appendix 4: Incorporating Patient Input into a Benefit-Risk Assessment Framework for Pulmonary Arterial Hypertension

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.³ 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 that can help inform the weighing the specific benefits and risks of a particular medical product under review.

The input provided by patients and patient representatives through the pulmonary arterial hypertension (PAH) 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 PAH below draws from various sources, including what was discussed at the pulmonary arterial hypertension Patient-Focused Drug Development meeting held on May 13, 2013. This sample framework contains the kind of information that we anticipate could be included in a framework completed for a drug under review for PAH. 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.

³ 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 Pulmonary Arterial Hypertension Benefit-Risk Assessment Framework

Dimension Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<ul style="list-style-type: none"> – Pulmonary arterial hypertension (PAH) is a life-threatening and progressive disease characterized by abnormally high blood pressure (hypertension) in the pulmonary artery. – Prevalence of PAH is estimated to be between 15 and 50 cases per 1 million adults, and it is more commonly diagnosed among women. – PAH symptoms may include shortness of breath, fatigue, weakness, chest pain, dizziness and fainting, heart palpitations, and swelling of the legs, ankles or abdomen. – Symptoms can have considerable detrimental effects on a patient’s quality of life, ability to function in daily activities, and overall social and societal engagement. 	<p>Pulmonary arterial hypertension is a rare and under-diagnosed condition more commonly diagnosed in women. It can rapidly take a significant physical and emotional toll on a patients’ quality of life routine and the ability of patients to engage in the activities of daily living.</p>
Current Treatment Options	<p>There are a number of FDA approved treatments for PAH:</p> <ul style="list-style-type: none"> ○ Endothelin Receptor Antagonists (ERAs) – ERAs are a class of drugs that help to prevent blood vessels from narrowing. Commonly prescribed ERAs include Letairis (ambrisentan), Tracleer (bosentan), and Opsumit (macitentan). Common side effects across these three drugs are respiratory issues (including nasal stuffiness and respiratory infections), headaches, and fluid retention. See individual label for specific side effects. ○ Phosphodiesterase type 5 Inhibitors (PDE 5 Inhibitors) – PDE 5 Inhibitors are a class of drugs that allow the lungs to produce more of their own vasodilators. Commonly prescribed PDE 5 Inhibitors include Revatio (sildenafil) and Adcirca (tadalafil). Common side effects across these two drugs include headaches, flushing of the skin, pain and muscle aches, respiratory issues, and stomach issues. See individual label for specific side effects. ○ Prostacyclins are a class of drugs that relieve shortness of breath. Commonly prescribed inhaled prostacyclins include Ventavis (iloprost) and Tyvaso (inhaled treprostinil). Commonly prescribed intravenous (IV) prostacyclins include IV Remodulin (treprostinil), Flolan (epoprostenol), and Veltri (room temperature stable epoprostenol). Commonly prescribed subcutaneous prostacyclins include subcutaneous treprostinil (Remodulin). Common side effects across prostacyclins include flushing of the skin, cough, headaches, nausea, pain (i.e. jaw, muscles, joints), passing out, and blood pressure changes. See individual label for specific side effects, including side effects based on route of administration. <ul style="list-style-type: none"> – Other treatments used off-label include calcium channel blockers, digoxin, diuretics, oxygen therapy, and warfarin. – Medical and surgical procedures such as lung transplant, heart-lung transplant, and atrial septostomy can prolong survival and improve quality of life, but may result in complications such as organ rejection, infection, death, and more. – Many patients include pulmonary rehabilitation, diet and exercise modification, and other lifestyle changes as part of their treatment regimen. 	<p>Drug treatments that slow the progression of the disease are available for PAH patients; however, efficacy varies from patient to patient, and significant side effects can limit benefits or preclude use of these medications. Additionally, frequency of dosing and route of administration can often be burdensome on patients. Thus, there is a continued need for additional effective and tolerable treatment options for patients to improve their daily functioning and increase life expectancy.</p>