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

Idiopathic Pulmonary Fibrosis

Public Meeting: September 26, 2014
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Center for Drug Evaluation and Research (CDER)
U.S. Food and Drug Administration (FDA)

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Introduction

On September 26, 2014, FDA held a public meeting to hear perspectives from people living with idiopathic pulmonary fibrosis 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 (FY) 2013 - 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 idiopathic pulmonary fibrosis

Idiopathic Pulmonary Fibrosis (IPF) is a rare, chronic, progressive, interstitial lung disease of unknown etiology affecting around five million patients worldwide, affecting more men than women. Patients are generally middle-aged or older at time of diagnosis. Disease progression is variable but progressive fibrosis (scarring) leads ultimately to death, with a median survival of 3 to 5 years after diagnosis. Symptoms often include dyspnea (shortness of breath), non-productive (dry) cough, unintended weight loss, fatigue, and clubbing of the fingers and toes, among others. Over time, IPF can lead to a debilitating loss of physical ability, often leading to patients being unable to care for themselves.

The goals for the treatment of IPF are to reduce symptoms and signs, improve quality of life, slow/halt disease progression, and increase survival. At the date of this meeting (September 26, 2014), there were no approved therapies specifically for the treatment of IPF and the slowing of disease progression.[1] Prednisone, azathioprine, and N-acetylcysteine (NAC) have been used to treat IPF symptoms, but generally do not significantly increase life expectancy. Lung transplantation is an option for some patients and may improve quality of life and life expectancy. Other treatments that alleviate symptoms include oxygen therapy and pulmonary rehabilitation.

Meeting Overview

This meeting provided FDA the opportunity to hear directly from patients, patient caregivers, and patient representatives about their experiences with IPF and its treatments. Discussion focused on two key topics: (1) symptoms that matter most to patients and their impact on daily life and (2) patients' perspectives on current approaches to treating IPF. The questions for discussion (*Appendix 1*) were published in the Federal Register notice[2] 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),*

[1] Since this date, two drug products have been approved by FDA for the treatment of IPF. These include Ofev (nintedanib) and Esbriet (pirfenidone), both approved October 15, 2014.
[2] http://www.gpo.gov/fdsys/pkg/FR-2014-07-08/pdf/2014-15871.pdf

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 40 idiopathic pulmonary fibrosis patients or patient representatives attended the meeting in-person, and approximately 20 patients or patient representatives provided input through the live webcast and polling questions. According to their responses to the polling questions, around two-thirds of these participants were or were speaking on behalf of men. In-person patient participants ranged from 40 to over 80 years old. Although participants at this meeting may not fully represent the IPF patient population, FDA believes that the input received reflects a range of experiences with IPF.

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 IPF 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, the webcast, and the docket comments emphasized the challenge of living with IPF, its impact on daily life, and the difficulties involved in treating IPF. Several key themes emerged from this meeting:

- IPF is a life-threatening, debilitating disease that places a significant burden on daily life and has a severe impact on how patients feel and function. Most participants focused their comments on shortness of breath, severe coughing, and persistent fatigue as the most burdensome aspects of their disease. These symptoms often worsen over time, making patients less able to move and care for themselves. Participants emphasized how the terminal nature of IPF takes an enormous toll on patients and caregivers both physically and emotionally.

- Daily life for IPF patients revolves around managing their IPF symptoms and treatments. Participants described severe limits on mobility, difficulty with basic tasks requiring exertion, difficulty interacting with friends and family, emotional impact on patients and caregivers, stigma, and financial and job impacts. Participants stressed that they had lost many things they had loved in life because of their disease.

- Participants shared their experiences with prednisone, steroids, and oxygen therapy, all of which had varying degrees of success in managing symptoms. Participants largely focused on the downsides of these treatments and emphasized their desire for treatments that slow disease progression, better address the underlying lung scarring, and provide better control of supplemental oxygen. Many participants stated that they would like the opportunity to consider a lung transplant, but that it was not a feasible option for them; they stressed the difficulty of living with a disease with no cure, or holding out hope for a transplant they were unlikely to receive.

This report summarizes the input received and details the experiences of the meeting participants. The input generated through this Patient-Focused Drug Development meeting strengthens our

understanding of the burden of IPF on patients and their experiences and perspectives on treatments for IPF. FDA will carefully consider this input as it fulfills its role in the drug development process, including when advising sponsors on their drug development programs and when evaluating products for marketing approval. For example, Appendix 4 shows how this input may directly support our benefit-risk assessments for products under review. This input may also be of value to the drug development process more broadly. For example, drug developers may find the input from meeting participants on the benefits and downsides of their existing treatments useful when exploring potential areas of development. It could identify opportunities for improving existing treatments such as oxygen therapy, as well as opportunities to develop and qualify better outcome measures in future clinical trials.

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

The first discussion topic focused on patients' experiences with their IPF symptoms and the impact these symptoms had on their daily life. FDA was particularly interested in hearing patients describe specific activities they could no longer do at all, or as fully as they would like, because of their condition.

Four panelists provided comments to start the dialogue, including two patients currently living with the disease and two caregivers speaking on behalf of their spouses who had died from IPF. The panelists described the difficulty of living with IPF and the physical, emotional, and social impact IPF symptoms have on many facets of daily life. They described feelings of anxiety, depression, and fear associated with being diagnosed with a terminal disease with few treatment options. In the large-group facilitated discussion that followed the panel discussion, the majority of the patients, caregivers, and patient representatives attending the meeting indicated by a show of hands that they shared the experiences of the panelists.

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. Coughing, shortness of breath, and fatigue or malaise received the highest number of responses. Participants attending via webcast reported results similar to those expressed by in-person participants. The facilitated discussion explored these and other symptoms in more detail and provided an opportunity for those in the audience to share their perspective. The symptoms discussed by in-person and web participants are described in more detail below.

Coughing

Coughing was mentioned by over three-fourths of in-person and web participants as being one of their most significant symptoms. Some participants described "coughing fits" as prolonged periods of dry, hacking coughs. One participant shared that her father's "debilitating" and "violent" coughing fits would result in him being unable to catch his breath. Participants described an inability to control their coughing, often leading to episodes of shortness of breath, hypoxia, or exhaustion. One caregiver described that her husband's cough sounds like "something is caught in his throat. It's like he's unable to finish one cough." Some participants shared experiences with wet, productive coughs. One webcast participant commented that their wet coughs produced "thick, sticky mucous … resulting in hacking and spitting." Another caregiver described her father's wet coughs required oral suctioning for secretions which made him "feel like he was choking."

Participants identified several triggers that can result in extended episodes of coughing, including:

- **Physical activity** – Walking, climbing stairs, personal care, household chores, or any effort that resulted in being short of breath

- **Weather-related issues** – Barometric pressure, humidity, dust, and high temperatures

- **Speaking and expressing emotion** – Talking or clearing the throat during conversation, laughing, and crying

- **Other triggers** – Time of day, secondhand smoke, strong smells, not swallowing food properly, and chest discomfort (identified as a "tickle" in the chest)

A few participants described the worsening of their coughing symptoms over time. One caregiver noted that his wife's coughing worsened over a period of years, sharing that eventually she "couldn't catch her breath. She couldn't stop coughing." Another participant commented on his experience of dealing with coughing for years before a formal diagnosis, and that his cough progressed from "sounding like a sneeze" to a stronger, deeper cough.

The following examples illustrate the experiences shared by in-person meeting participants:

- "On my worst days, coughing will wipe you out for an entire day … Physically, you're exhausted."

- "My cough was really so deep that it felt like I broke my ribs, and my ribs became so cramped that I couldn't even twist [my body]."

- "[My cough] comes with exertion … walking up a flight of stairs … putting your clothes on, bending over and tying your shoes, fixing something in the kitchen, moving around."

- One caregiver shared that his wife would "just be soaking wet [from sweat]" after a coughing fit.

Participants also shared the resulting impacts of coughing fits. These included exhaustion, nausea, and ear disorders (including hearing loss and pain in the ears). One participant noted that coughing disrupted his sleep, saying "I can only sleep … for maybe an hour and a half or two hours before I have to get up and cough."

Shortness of breath

Nearly all in-person and webcast participants identified shortness of breath as one of their most significant symptoms. For most participants, the severity of their shortness of breath had a major impact on daily life and overall health. Participants described intense episodes of difficulty breathing, including one caregiver who shared that her husband's struggle to breathe left him looking "like he was going to pass out." Another caregiver shared her husband's frustration with shortness of breath and how it affected his ability to walk and perform physical activities (such as climbing stairs or performing housework). This comment resonated with other participants who shared similar experiences of shortness of breath or wheezing after minimal exertion, including one participant who explained, "[even] on my very best days … it's hard to talk and be able to breathe." Another participant said her husband would look "white and pasty" after experiencing shortness of breath. Additionally, some participants associated their shortness of breath as a normal outcome of coughing fits. One participant explained that even "little coughing spells" could cause him to be out of breath.

The following examples illustrate the experiences shared by meeting participants:

- "What I did feel was a very tight noose around my neck … It was extremely difficult, and I kept scratching at my throat, trying to pull that invisible noose off … I couldn't do a flight of steps without being out of breath."

- One participant described feeling like she was underwater when having a severe shortness of breath episode, saying "…when it was the worst panic of the moment … I suddenly knew what it was like to drown."

- "…When I get out of the shower … I'm panting for breath just by toweling off."

Several participants also indicated that their shortness of breath worsened over time, which consequently increased their reliance on supplemental oxygen. A few participants said that within time frames of a few months to a year after diagnosis, they needed to be on oxygen constantly to manage their shortness of breath. Other participants had similar experiences, including one who described her husband's loss of "ten percent of his lung capacity" over the span of a few months, resulting in him needing supplemental oxygen constantly.

Fatigue

Over half of in-person participants and web participants identified fatigue as being one of their most significant symptoms. Participants commonly associated fatigue with physical exertion, shortness of breath, and coughing. Participants stated that their fatigue can manifest in a variety of ways, such as physical fatigue, including muscle fatigue, persistent lack of energy, and overall malaise. One caregiver shared her mother's experiences with fatigue, saying her legs "felt like Jell-O" and she constantly experienced a lack of energy unrelated to sleepiness; this comment resonated with many meeting participants. One participant identified fatigue as being a constant difficulty for her, saying, "the fatigue really weighs on you … you're completely exhausted."

Other participants commented that fatigue was related to sleep issues, including sleep disturbances and unrefreshing sleep. Several participants described feeling sleepy or exhausted during the day and noted the importance of a day-time nap, even after a full night's sleep. One participant described her mother falling asleep during the day "as soon as she sat down." Others shared their difficulty with falling asleep, describing being physically exhausted but mentally awake. This included one participant who said despite her exhaustion, her brain would be "going a million miles a second".

Fatigue was also generally associated with cognitive effort (such as concentrating on computer-based tasks), and as a result of shortness of breath and coughing. Descriptions of fatigue after struggling to breathe ranged from simply feeling "tired" to being "completed exhausted." Another participant described the exhaustion that follows strong coughing fits as being capable of "just literally wiping you out." Finally, one webcast participant noted that fatigue had developed over time and became a significant symptom after the disease had progressed.

Other symptoms

In addition to shortness of breath, coughing, and fatigue, participants also identified a range of other symptoms. These included:

- **Pain** – Pain was described in a variety of ways, including headaches, chest pain, tightness in the chest, pain from clubbing in the extremities, and localized pain in the lips and tongue. As one participant described his difficulty with joint pain, "my fingers hurt too much to push down on the [camera] shutter."

- **Gastrointestinal Issues** – Several participants reported suffering from a range of gastrointestinal issues. Acid reflux and associated issues such as irritation of the throat and larynx, exacerbated coughing, and reflux going into the lungs were among the most commonly mentioned symptoms. Other symptoms identified included nausea and constipation.

- **Anxiety and Depression -** A few participants mentioned depression and anxiety as a result of living with and managing their IPF. Some patients reported feelings of anxiety or panic after episodes of shortness of breath or coughing. Others linked their feelings of depression to the difficulty of living with a terminal illness.

- **Complications of IPF** – Several participants mentioned experiencing complications related to their IPF which required hospitalization, including pneumonia and infection.

- **Co-morbid conditions** –Participants discussed pulmonary hypertension and heart failure as co-morbid conditions.

Overall impact of IPF on daily life

Participants described the physical, social, and emotional impact that living with IPF has had on their lives, including:

- **Managing work and home life.** The most frequently mentioned impact on daily life was the decrease of physical function. This included struggling to perform basic activities such as walking up stairs, showering, housework, and other everyday tasks. One participant explained, "It's difficult to keep my house clean … I get very tired, so it's sweep the floor, sit down and rest for a long time." Another described the process of getting dressed as "an hour-and-a-half struggle." One caregiver described her mother's experiences, saying that "the inability to get up and move around when she wanted [to]" resulted in depression.

- **Impact on work and careers.** For example, one participant shared that he needed an early retirement, as he was unable to deal with the fatigue and the shortness of breath while working.

- **Giving up the things they love.** For many, the difficulty with physical activity meant discontinuing hobbies they once enjoyed. One participant had to give up hobbies such as horseback riding and photography, sharing, "I have a great deal of difficulty walking [and] lugging the oxygen, lugging the camera."

- **Stigma**. Participants also described the reactions they experience in public places, especially when coughing, when others viewed them as contagious and maintained a distance. One participant said that her husband could "clear a crowd" when he had a coughing fit. Others felt

embarrassed that their coughing was impacting those around them. One participant shared that she brought a washcloth to work in order to muffle her cough, so she wouldn't be "bothering other people." Another described coughing in public as one of her husband's "most difficult and embarrassing issues."

- **Isolation and impacts on relationships.** Participants shared the impact their disease had on their social lives and ability to interact with friends and family, including one webcast participant who described her father's sadness at not being able to be an active grandfather. Some participants also expressed difficulty talking about their condition to people close to them because of the seriousness of the disease, adding to a feeling of loneliness. Some shared that since they did not outwardly look sick, it was difficult for others to understand the debilitating impact of their disease. One participant described her IPF by saying, "It's a very lonely disease. It's a very lonely place to be, because it is terminal."

Topic 2: Patient Perspectives on Treatments for IPF

The second discussion topic focused on patients' experiences with therapies used to treat their IPF. Four panelists provided comments to start the dialogue. Two were patients who had been living with IPF for over ten years (and were also lung transplant recipients), and two were caregivers of family members who had passed away from IPF. In the large-group facilitated discussion that followed, experiences voiced by participants were largely similar to the comments shared by panelists. The majority of participants indicated by a show of hands that their experiences (or those of loved ones) were similar to the panel discussion. Following the panel discussion, there was a facilitated discussion examining participants' perspectives with managing treatments and the challenges they face in finding effective treatments.

In the discussion that followed, participants identified and described their current treatment regimen. Participants mentioned a wide range of treatments they used, including prescription drug therapies, medical procedures, and other investigational and non-drug therapies. While many participants acknowledged that their treatments were necessary and helpful for symptom management, several participants felt their treatment regimens provided little relief or had significant downsides.

Participants also provided their perspectives on an ideal therapy for IPF, including the need for better understanding of IPF for proper diagnosis and treatment.

Prescription and over-the-counter drug therapies

According to a polling question (Appendix 3, Q7), most participants reported taking drug therapies for the management and alleviation of their IPF symptoms. The two most commonly mentioned therapies used were oxygen therapy and prednisone.

Oxygen therapy

The most common treatment mentioned by participants was the use of oxygen therapy as an integral part of their treatment regimen to alleviate their shortness of breath. Participants described that continuous flow of supplemental oxygen was critical; as one participant shared, oxygen therapy was a "matter of life and death." Several participants emphasized how their daily life revolved around constantly ensuring they had access to oxygen. For many participants, the importance of oxygen therapy increased rapidly over time. One participant noted that within a year of his diagnosis, he was "on oxygen 24/7" to manage his shortness of breath. Another participant doubled his oxygen flow from two to four

liters of continuous flow over the course of a year. Participants also noted the trial and error process of identifying the proper type of oxygen therapy equipment that best suited their needs.

However, most comments regarding oxygen therapy highlighted the burdensome nature of the treatment. The most commonly mentioned downside was the impediment oxygen tanks posed to participating in activities. Participants described being unable to travel because of their constant need for supplemental oxygen. Others noted how increasing oxygen needs gradually reduced their mobility and eventually left some participants housebound. One participant shared that "needing oxygen is like being in jail." Participants also described that oxygen therapy equipment (such as oxygen tanks and concentrators) significantly impacted their ability to move; one caregiver noted that her father had to move out of a two story home to avoid steps, while another had to use a golf cart to transport his oxygen therapy equipment. One participant described her father's dependence on supplemental oxygen by saying he was "tethered [to the] oxygen machine at his home, and getting outside was pretty much impossible."

When discussing the burdensome impact of oxygen therapy their lives, participants also mentioned some of the side effects of their oxygen therapy. One participant mentioned suffering from "brain freeze" whenever she used liquid oxygen. Other downsides included headaches, dry lips, irritated nose, and dry mucous.

Prednisone

Prednisone, an anti-inflammatory corticosteroid, was mentioned by several participants both in the meeting and on the webcast as being a part of their treatment regimen. Participants provided mixed experiences with prednisone; while some participants described that prednisone was effective in treating shortness of breath, others noted that prednisone was had little to no effect.

Several webcast participants noted that prednisone was generally effective and did not pose significant side effects. One participant described how prednisone helped with the "crackling in [the] lungs." Another participant, after reducing his prednisone dosage, said he experienced "deeper fatigue and more shortness of breath." However, participants also mentioned downsides to treatment. A few participants described a feeling of "prednisone fog" due to cognitive impairment and an inability to think clearly while taking the medication. Others said that prednisone "did not work at all" and was "a hard medication on your mind and body." One participant shared that prednisone was impacting their sleep cycle and ability to sleep.

Other side effects included the significant weight gain that resulted from prednisone therapy, including one woman who shared, "the prednisone blew me up 30 pounds within two months." One participant focused on the behavioral changes the prednisone had on her father: "The most concerning response was the change in his demeanor … he became irritable and argumentative." The same participant also noted that her father had experienced trouble with his teeth that he attributed to the prednisone use. A few participants noted that prednisone treatment was ineffective and that they or their loved ones had to discontinue treatment.

Other drug therapies

A range of other drug therapies were also mentioned during the meeting. These included:

- **Other steroid treatments** – Steroids treatments were identified by several patients as an option for targeting symptoms such as shortness of breath. Participants reported taking multiple courses of steroid treatments; in some cases, participants shared they had to discontinue treatments as they became ineffective over time. One participant shared that after being taken off steroids, "my breathing became extremely difficult." Other participants described side effects of treatment including one caregiver who noted that her father "seemed to grow more fragile on steroids." Another participant noted the increased difficulty in breathing after a steroid treatment.

- **N-Acetylcysteine (NAC)** – Several participants mentioned taking NAC as part of their treatment regimen. Perspectives were mixed, with most participants having little to no relief taking NAC. One participant noted that NAC provided effective relief, sharing that when he stopped treatment for a few days, his coughing noticeably increased. Another participant was unsure if NAC therapy was effective for her, but felt that it did help her breathing and coughing. One participant shared that the smell and taste of NAC made it difficult to tolerate.

- **Pirfenidone**[3] – A few participants described their experiences participating in clinical trials for pirfenidone. One webcast participant who had taken pirfenidone for a year shared that "a recent CT scan showed that the disease hasn't progressed."

- **Cough medicine –** Several cough medicines were identified by participants. These included prescription therapies such as **Tussionex PennKenetic** (hydrocodone), **benzonatate**, and **inhalants.** In addition, participants reported taking **Mucinex DM** and other **over-the-counter cough medications**. Several participants shared that cough medicines were beneficial, including one participant who said they helped "clear [coughing] up for the whole day." Other participants focused on the cognitive side effects associated with their cough medicine. One participant described her husband being in an "intoxicated state" after taking cough medicines. Another caregiver on the webcast shared a similar experience, noting that cough medicine would "impair" her husband and made him reluctant to take it.

- **Acid reflux medications** – Several participants described taking medication (such as Prilosec) to treat their acid reflux. One participant shared, "If I don't take my acid reflux medicine, I'm miserable. It makes that much of a difference." Some participants mentioned that they were primarily taking acid reflux medication as a preventative measure.

- **Other treatments** – Participants mentioned taking several other treatments to treat symptoms of IPF or co-morbid conditions, including, in their words, Lasix (furosemide), Adcirca (tadalafil), Gleevec (imatinib), Atrovent (ipratropium bromide), albuterol, azathioprine, video-assisted thoracoscopic surgery (VATS), potassium, antibiotics, immunosuppressants, and anxiety

[3] Esbriet (pirfenidone) was approved by the FDA for the treatment of idiopathic pulmonary fibrosis (IPF) on October 15, 2014.

medication. Some participants mentioned taking a combination of treatments, but were unable to determine if they were working because symptoms weren't improving.

Lung transplant

Several participants shared their considerations on undergoing a lung transplant. Three in-person participants shared their experiences with receiving a lung transplant. One participant described her experience with a complicated transplant, one that resulted in colon damage and a viral infection. She also shared the side effects she experienced taking anti-rejection medications, including memory loss, tremors, confusion, migraines, sensitivity to sun, thinning hair, chronic fatigue, depression, anxiety, and flu-like symptoms.

Most discussed the challenge of waiting for a transplant, focusing on the length of the wait and the shortage of donor organs. Several described the difficulty of having limited or no treatment options other than a lung transplant. Caregivers expressed a feeling of helplessness of waiting for a lung transplant while their loved ones' symptoms worsened. As one caregiver described, "[The] only one treatment currently out there … is a lung transplant. That's hard to take." Another said that the knowledge of being on a transplant recipient list could be a source of hope, saying that in her husband's final days the hope of getting a transplant was something "he hung on to."

Non-drug therapies

In addition to the medical treatments, several participants mentioned the importance of non-drug therapies as part of their treatment regimen. The most commonly mentioned was pulmonary rehabilitation, which helped several patients adapt their daily life to their reduced lung capacity. Several participants commented that pulmonary rehabilitation helped them strengthen their lungs, and participate in activities longer than they could otherwise. One caregiver shared that after a rehabilitation session, her husband's stamina would increase and he was "able to do some things a lot longer … [he was] not as fatigued." Other participants shared that going through rehabilitation was mentally and emotionally empowering. One participant noted that he found support in being "with others that have the same issues and understand what I'm going through."

Participants also mentioned a range of other non-drug therapies, including light exercise, diet changes, supplemental vitamins, crushed ice (to help stop coughing), and humidity and temperature control. Some participants described holistic approaches to therapies including reiki, acupuncture, massage, meditation, and prayer.

Perspectives on an ideal treatment

Participants also provided their perspectives regarding improvements to existing drug regimens and developing an ideal treatment for IPF. Participants commented that absent a cure, they hope for a treatment that can slow disease progression, mitigate the impact of the most significant symptoms of IPF, and improve their quality of life. As one participant noted, "If we can't solve this problem today, let's do something that improves patient symptoms, that improves their quality of life, that can help them to move forward, at least for a little bit of time with their families." Another participant shared that having more treatment options to slow progression would "give patients hope where they have none."

Other participants focused on improving oxygen therapy, which they identified as a critical part of treatment regimens, but one that had a burdensome impact on quality of life and everyday tasks. Participants expressed a desire for overall improvement in oxygen therapy, such as making oxygen delivery systems more convenient to use and travel with, increased control of oxygen flow, and other options for breathing without oxygen. One participant said, "I wanted to be untethered more than anything. To be attached to that machine or to a tank is not a pleasant experience."

Other considerations on treatments

Several participants focused on a perceived lack of awareness and medical knowledge of IPF by medical professionals. Participants highlighted two examples in which this lack of awareness negatively impacted them: improper treatment in the emergency room and misdiagnoses of IPF. One participant described an experience he had in the emergency room when he was given incorrect therapy, saying: "I wasn't in respiratory failure … and then all the liquid went around my heart and lungs, and within 24 hours, I was almost dead."

Others shared that prior to receiving a formal diagnosis of IPF they were incorrectly diagnosed with conditions such as emphysema. One participant described her father's experience with an incorrect diagnosis, saying "my father's treatment began six months before he was diagnosed with IPF, because he was treated symptomatically for cough and for shortness of breath with inhalers … that had absolutely no effect on his symptoms." Participants said that this lack of understanding was a problem that should be addressed by the healthcare community in the future.

Summary of Comments Submitted to the Public Docket

FDA received 35 comment submissions to the public docket that supplemented the Patient-Focused Drug Development meeting on IPF. The majority of the comments were submitted by IPF patients and caregivers. Twelve comments were submitted by advocates or healthcare professionals, including three surveys submitted by advocacy organizations: the Pulmonary Fibrosis Foundation, PatientsLikeMe, and the Coalition for Pulmonary Fibrosis (in partnership with Genetic Alliance). These surveys examined patients' and caregivers' perspectives on their most significant symptoms, the impact of IPF on patient's quality of life, patients' treatment options, and other issues.

The docket comments reflected the experiences and perspectives shared at the meeting on the symptoms that affected their lives the most, the impacts of their disease on daily life, and their experiences with treatments for IPF. The following is a brief summary of their comments.

Submitted comments on symptoms of IPF

Comments submitted to the public docket reflected those received during the meeting on the burdensome nature of IPF. The symptoms of IPF mentioned on the docket reflected those discussed during the meeting. The most commonly mentioned symptoms include:

- Shortness of Breath
- Cough
- Acid Reflux / GERD
- Fatigue
- Chest Pain / Tightness
- Sleep issues

Other symptoms identified by docket commenters or in the submitted surveys included muscle spasm, salty taste in mouth, nose bleeds, weight gain, and high blood pressure. A few co-morbid conditions were also identified by participants, including idiopathic autoimmune hemolytic anemia (IAHA), renal

cell cancer, and pulmonary hypertension. The submitted surveys were also consistent with input received during the meeting. For example, respondents to the Pulmonary Fibrosis Foundation survey identified shortness of breath, fatigue, and coughing as the most significant symptoms for survey respondents. The survey submitted by The Coalition for Pulmonary Fibrosis were also similar, with patients listing coughing, fatigue, shortness of breath, and chest or back pain even on their best days.

Commenters echoed input from meeting participants on the impact of shortness of breath. As one commenter described, "there is nothing like shortness of breath, that gasping feeling and unable to get the air you need, to send you into panic mode. It's a horrible feeling." Others shared their experiences becoming short of breath after minor physical activity, finding it difficult to perform basic tasks. Additionally, a few commenters mentioned that their shortness of breath worsened over time.

Other commenters reemphasized that fatigue was one of their most significant symptoms. Similar to the perspective shared by meeting participants, commenters expressed an overall general fatigue and lack of energy, as well as becoming tired easily after minimal exertion. A few commenters also described fatigue resulting from lack of restful sleep, including one who shared, "it is like I can never get enough sleep … I [always] wake feeling exhausted." Another commenter shared that his fatigue worsened on warm days.

A few commenters also emphasized the burden of coughing. One commenter noted that coughing (which produced phlegm) was related to time of day, worsening at night time. Another described his exhaustion and inability to control or stop his coughing fits.

Submitted comments on the overall impact of IPF on daily life

The docket comments reiterated the burden that IPF and its symptoms have on daily life, such as the decrease in physical function. Many described how physical activity, including walking and climbing stairs, exercise, hobbies, and household tasks, were a struggle due to IPF symptoms. Survey results generally reflect this input. For example, over half of respondents to the PatientsLikeMe survey said that IPF interfered "a lot" or "extremely" with their daily activities at work or home. Others commented on the difficulty of traveling with IPF because of reliance on oxygen therapy. One commenter also addressed the emotional toll of being a caregiver for a family member with IPF, and the difficulty of watching them "try to hang on to their life."

Submitted comments on treating IPF

The comments submitted to the docket reflected the difficulty of managing symptoms for a condition with few treatment options. Similar to the public meeting, the therapies mentioned by docket participants included oxygen therapy, pirfenidone, prednisone, N- Acetylcysteine (NAC), reflux medication. Other medications mentioned included antibiotics, Actimmune (interferon gamma-1b), Revatio (sildenafil), and omeprazole. Medical procedures mentioned included lung transplant and nissen fundoplication. Non-drug therapies mentioned included dietary changes, exercise, and pulmonary rehabilitation.

The discussion of oxygen therapy closely resembled input received at the public meeting. Commenters reiterated the importance of oxygen therapy in managing their shortness of breath and other IPF symptoms. Some commenters described how portable oxygen allowed them to remain mobile and to travel. One participant said she would be unable to function well without oxygen therapy. Some, however, echoed the desire to be less dependent on supplemental oxygen, calling it a burden on everyday life.

Several perspectives were provided on ideal treatments for IPF. One aspect of an ideal treatment that commenters provided was for a treatment to slow the progression of the disease, or reverse the progress of the scarring on the lungs. Others mentioned that they would like to see improvements in preventing constant coughing and providing better monitoring and control of oxygen flow.

Conclusion

The Patient-Focused Drug Development meeting on IPF provided the FDA an important opportunity to obtain patients' in-depth point of view on the severity of IPF, its impact on daily life, and available treatment options. IPF is a progressive, terminal disease that severely impacts a patient's day-to-day functioning and has a devastating impact on their lives and the lives of their caretakers. Participants described becoming increasingly debilitated while losing much of their physical function, and ability to care for themselves, and ability to participate in activities. Treatments, with the exception of lung transplants, are focused on mitigating symptoms rather than treating the disease itself. Participants expressed a strong desire for improvements to their existing treatments and for new treatments that better target the underlying cause of IPF. FDA shares the patient community's commitment to furthering the development of safe and effective drug therapies for IPF.

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. FDA is truly grateful to all of the participants who shared their experiences and challenges living with IPF as well as their hopes for the future, as exemplified in the two quotes below:

> *"We have come together by our disease … and I want all of you [participants] to know how brave and courageous you are for sharing your story and being vulnerable and allowing others into your world, because I know how tough that is."*

> *"My goal is to make sure that by the time she's older, [my 4-year old daughter] says, "Pulmonary fibrosis is something that killed people in the old days, and people don't die of it anymore."*

Appendix 1: Meeting Agenda and Discussion Questions

Public Meeting on Idiopathic Pulmonary Fibrosis Patient-Focused Drug Development

September 26, 2014

12:00 – 1:00 pm	Registration
1:00 – 1:05 pm	Welcome Soujanya Giambone, MBA *Office of Strategic Programs (OSP), Center for Drug Evaluation and Research (CDER), FDA*
1:05 – 1:10 pm	Opening Remarks Lydia Gilbert McClain, MD, FCCP *Deputy Directory, Division of Pulmonary, Allergy and Rheumatology (DPARP), CDER, FDA*
1:10 – 1:20 pm	Overview of FDA's Patient-Focused Drug Development Initiative Theresa Mullin, PhD *Director, OSP, CDER, FDA*
1:20 – 1:30 pm	Background on Disease Area and Treatment Banu Karimi-Shah, MD *Team Lead, DPARP, CDER, FDA*
1:30 – 1:40 pm	Overview of Discussion Format Soujanya Giambone, MBA *OSP, CDER, FDA*
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 IPF. A panel of patients and patient representatives will provide comments to start the discussion.
3:40 – 4:25 pm	Large-Group Facilitated Discussion on Topic 2 Patients and patient representatives in the audience are invited to add to the dialogue.
4:25 – 4:55 pm	Open Public Comment
4:55 – 5:00 pm	Closing Remarks Banu Karimi-Shah, MD *DPARP, CDER, FDA*

Discussion Questions

Topic 1: 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 shortness of breath, cough, fatigue, 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 treatment approaches

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 well does your current treatment regimen treat the most significant symptoms of your disease?

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) Because 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

- Faye MacInnis – Caregiver
- Laura Roix – Patient
- Curtis Thompson – Caregiver
- Diane Reichert – Patient

Patient Panel, Topic 2

- Heather Snyder – Patient
- Michael Henderson – Patient
- Taleena Koch – Caregiver
- Teresa Barnes – Caregiver

FDA Panel

- Lydia Gilbert McClain, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP), CDER
- Banu Karimi-Shah, DPARP, CDER
- Sally Seymour, DPARP, CDER
- Ashley Slagle, Study Endpoints and Labelling 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 26, 2014, Idiopathic Pulmonary Fibrosis Patient-Focused Drug Development meeting. Participation in the polling questions was voluntary. There results were used as a discussion aid only and should now be considered scientific data.

Demographic Questions – Asked during "Overview of Discussion Format" Session

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 idiopathic pulmonary fibrosis?

    a. Yes
    b. No

3. What is your age / your loved one's age?

    a. Younger than 30
    b. 31 – 40
    c. 41 – 50
    d. 51 – 60
    e. 61 – 70
    f. 71 – 80
    g. 81 or greater

4. Are you / Is your loved one:

    a. Male
    b. Female

5. What is the length of time since your diagnosis?

    a. Less than 1 year ago
    b. 1 year ago to 3 years ago
    c. 3 years ago to 5 years ago
    d. More than 5 years ago

Question for Topic 1

1. Of all the <u>symptoms</u> you have experienced because of idiopathic pulmonary fibrosis, which do you consider to have the <u>most significant impact on your daily life</u>? **Please choose up to three symptoms.**

a. Shortness of breath
b. Fatigue or malaise
c. Coughing, especially dry or hacking coughs
d. Chest pain
e. Gradual, unintended weight loss
f. Decreased appetite
g. Clubbing, (the widening and rounding of the tips of the fingers or toes)
h. Depression
i. Other symptoms not mentioned

Question for Topic 2

1. Have you ever used any of the following drug therapies to help reduce the symptoms of idiopathic pulmonary fibrosis? Check all that apply.

    a. Pulmonary rehabilitation
    b. Corticosteroids
    c. Immunosuppressants
    d. NAC (N-acetylcysteine)
    e. Investigational therapy
    f. Other prescription medicines (e.g. acid reflux therapy, inhalers)
    g. I'm not sure

6. Besides your drug therapies, what else are you doing to help reduce your symptoms of idiopathic pulmonary fibrosis? Check all that apply.

    a. Oxygen therapy
    b. Surgery (such as lung transplantation)
    c. Lifestyle changes, such as limit activity, changes in your home
    d. Other therapies not mentioned
    e. I am not doing or taking any therapies to treat symptoms

Appendix 4: Incorporating Patient Input into a Benefit-Risk Assessment Framework for IPF

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

In the Framework, the *Analysis of Condition* and *Current Treatment Options* rows summarize and assess the severity of the condition and therapies available to treat the condition. The assessment provides an important context for drug regulatory decision-making, including valuable information 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 idiopathic pulmonary fibrosis (IPF) 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 IPF below draws from various sources, including what was discussed at the idiopathic pulmonary fibrosis Patient-Focused Drug Development meeting held on September 26, 2014. This sample framework contains the kind of information that we anticipate could be included in a framework completed for a drug under review for IPF. This information is likely to be added to or changed over time based on a further understanding of the condition or changes in the treatment armamentarium.

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

Sample Idiopathic Pulmonary Fibrosis Benefit-Risk Assessment Framework

Dimension Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	– Idiopathic pulmonary fibrosis (IPF) is a debilitating, incurable disease of unknown etiology characterized by tissue scarring (fibrosis) in the lungs. – Disease progression is variable but progressive fibrosis (scarring) leads ultimately to death with a median survival of 3 to 5 years after diagnosis. – Prevalence of IPF is estimated to be around 5 million patients worldwide, affecting more men than women. – IPF symptoms may include dyspnea (shortness of breath), non-productive (dry) cough, unintended weight loss, fatigue, and clubbing of extremities. – Over time, IPF can lead to a debilitating loss of physical ability, severely impacting a patient's ability to move or care for themselves.	Idiopathic pulmonary fibrosis is a chronic and ultimately terminal disease which takes a large physical and emotional toll on patients. Over time, it can significantly impact patient's quality of life and places a large burden on patients' ability to live normally.
Current Treatment Options	– Until recently, patients in the U.S. suffering from IPF had no drug treatment approved by FDA. FDA approved two treatments for IPF in October 2014, Ofev and Esbriet: o Ofev (nintedanib) - Ofev is a kinase inhibitor that blocks multiple pathways that may be involved in the scarring of lung tissue. The decline in forced vital capacity – the amount of air which can be forcibly exhaled from the lungs after taking the deepest breath possible – was significantly reduced in patients receiving Ofev. The most common side effects of Ofev are diarrhea, nausea, abdominal pain, vomiting, liver enzyme elevation, decreased appetite, headache, decreased weight, and high blood pressure. Ofev should not be taken by pregnant women or patients with liver problems. o Esbriet (pirfenidone) – Esbriet is an anti-fibrotic drug, which acts on multiple pathways that may be involved in the scarring of lung tissue. Esbriet also significantly reduces decline in forced vital capacity for patients with IPF. The most common side effects of Esbriet are nausea, rash, abdominal pain, upper respiratory tract infection, diarrhea, fatigue, headache, dyspepsia, dizziness, vomiting, decreased/loss of appetite, gastro-esophageal reflux disease, sinusitis, insomnia, decreased weight, and arthralgia. Esbriet is not recommended for patients with liver problems. – Other treatments are often used by IPF patients in order to help manage symptoms, including oxygen therapy, prednisone and other steroids, N-Acetylcysteine, over-the-counter and prescription cough medicine, and acid reflux medications. – Oxygen therapy plays a critical role in the management of IPF symptoms, most importantly shortness of breath. Oxygen therapy can also place a large burden on patients' daily life, as managing equipment (such as oxygen tanks) and constantly needing a source of supplemental oxygen can restrict patients' independence and mobility. – Lung transplant can prolong survival and improve quality of life but is often not a feasible option for patients, and may result in complications such as organ rejection, infection, or other serious side effects. – Patients also include pulmonary rehabilitation, exercise, diet modification, yoga, meditation, lifestyle changes, and other non-drug or alternative therapies as supporting therapies.	Drug treatments that alleviate or help manage symptoms of IPF are available; however, there is currently no cure or treatment that address the underlying cause of IPF. Additionally, current treatments may have burdensome side effects or other impacts on patients. There is a large unmet need for additional treatments that better target the underlying disease. There is also a continued need for treatments that better manage symptoms without significant side effects or impacts on daily life.