

# **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

## **Patients Who Have Received An Organ Transplant**

**Public Meeting: September 27, 2016**

**Report Date: April 2017**

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

## Table of Contents

<b>Introduction .....</b>	<b>3</b>
Meeting overview .....	4
Report overview and key themes .....	4
<b>Topic 1: Patient perspectives on post-transplant health effects.....</b>	<b>6</b>
Perspectives on Post-Transplant Benefits .....	6
Perspectives on Post-Transplant Health Effects .....	7
Overall Impacts on Daily Life.....	8
<b>Topic 2: Patient Perspectives on Transplant and Treatment Impacts .....</b>	<b>9</b>
Perspectives on current treatments .....	10
Perspectives on ideal treatments for organ transplantation.....	12
<b>Summary of Scientific Session.....</b>	<b>12</b>
<b>Conclusion.....</b>	<b>15</b>
<b>Appendix 1: Meeting Agenda.....</b>	<b>16</b>
<b>Appendix 2: Patient and FDA Panel Participants.....</b>	<b>21</b>
<b>Appendix 3: Meeting Polling Questions.....</b>	<b>22</b>
<b>Appendix 4: Incorporating Patient Input into a Benefit-Risk Assessment Framework for Organ Transplantation .....</b>	<b>26</b>

## Introduction

On September 27, 2016, the Food and Drug Administration (FDA) held a public meeting to hear perspectives from people who have received an organ transplant (hereafter referred to as patients), caregivers of patients, and other patient representatives. FDA conducted the meeting as part of the agency's Patient-Focused Drug Development (PFDD) initiative,<sup>1</sup> an FDA commitment under the fifth authorization of the Prescription Drug User Fee Act (PDUFA V) to 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>

The PFDD meeting was conducted in the morning, and in the afternoon of September 27, FDA continued with a scientific session (summarized on p. 12) to explore topics on medication adherence and experience with interventions to mitigate nonadherence. This session provided a platform for FDA scientific reviewers, researchers, and patients to share their perspectives and gather information on current approaches to management of transplantation and treatment adherence.

## Overview of Organ Transplantation

Organ donation and transplantation can be lifesaving, transformative, and restorative for patients facing a range of serious conditions. In 2015, over 25,000 people in the United States received an organ transplant. Annually, the most commonly transplanted organs in the United States include kidney, liver, heart, lung, pancreas, intestine, and multiple organs such as kidney/pancreas or heart/lung. Most transplanted organs are recovered from deceased donors, but a substantial contribution of kidneys, and to a lesser extent, partial liver organs come from living donors.

Organ transplantation requires pharmacologic and non-pharmacologic management before and after receipt. Post-transplant management typically addresses four main objectives: prevention of organ rejection by the recipient's immune system, treatment of the underlying medical condition, treatment of emergent complications of the immunosuppression (IS) regimen, including prevention and treatment of infections, and managing the adverse effects of the IS regimen and concomitant medications. Serious illness, graft loss and death can occur from a number of causes, including undetected infections in donor organs and tissues and IS regimens that are too high or too low. Medications to prevent and treat rejection include induction immunosuppression with intensive combination regimens, maintenance immunosuppression with less intensive combination regimens, and additional medications for treatment of acute organ rejection. Other treatments include medications to prevent and treat viral, bacterial, fungal and other opportunistic infections; medications for treating the underlying medical conditions that led to the organ failure (such as hypertension, diabetes, and hepatitis C); and medications that treat the emerging complications, including hypertension and new onset of diabetes.

---

<sup>1</sup> The Federal Register Notice for the Patient-Focused Drug Development Initiative can be found here: <https://www.gpo.gov/fdsys/pkg/FR-2015-07-02/pdf/2015-16359.pdf>

Adherence to treatment regimens is important for health outcomes of patients who have received organ transplants. Treatment regimens are often life-long, and are critical for the long-term health of the patients and transplanted organs. For many, adherence to treatment is a significant challenge due to the complexity of treatment regimens, side effects of treatments, and numerous other factors.

## Meeting overview

The organ transplantation PFDD meeting provided FDA with the opportunity to hear directly from patients, patient representatives, and patient advocates about their experiences and perspectives on managing their health post-transplant. The morning discussion focused on two key topics: 1) post-transplant health effects and impacts of organ transplantation on daily life, and 2) perspectives on current approaches to managing post-transplant treatment. The questions for the morning discussion (*Appendix 1*) were published in a [Federal Register notice](#) that announced the meeting.

For each topic, a panel of patients (*Appendix 2*) shared comments to begin the dialogue. Panel comments were followed by large-group facilitated discussions inviting comments from other patients and patient representatives in the audience. An FDA facilitator led the discussion, and a panel of FDA staff (*Appendix 2*) asked follow-up questions. Participants who joined the meeting via the live webcast (referred to in this report as web participants) also contributed comments. In addition, in-person and web participants were periodically invited to respond to polling questions (*Appendix 3*), which provided a sense of the demographic makeup of participants and how many participants shared a particular perspective on a given topic.

Approximately 25 patients or patient representatives (including caregivers and patient advocates) attended the meeting in-person. Approximately 25 patients or patient representatives provided input through the live webcast. Patient participants in the room and on the webcast ranged in age from 14 to 65 and older and were split evenly between men and women. Participants included kidney, lung, heart, liver, and pancreas transplant recipients. Approximately half of these participants received an organ transplant more than 10 years ago, and the other half received a transplant between 1 and 10 years ago. Although participants at this meeting may not fully represent the overall population of patients who have received an organ transplant, FDA believes that the input received reflects a range of experiences on post-transplant impacts and management approaches.

To supplement the input gathered at the meeting, organ transplant patients and others were encouraged to submit comments on the topic to a public docket,<sup>2</sup> which was open until November 27, 2016. Thirteen comments were submitted to the public docket, the majority by individual patients and patient advocacy organizations. One survey was submitted to the public docket by the Alpha-1 Foundation.

More information, including the archived webcast and meeting transcript, is available on the meeting website: <https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm495933.htm>.

## Report overview and key themes

---

<sup>2</sup> A *docket* is a repository through which the public can submit electronic and written comments on specific topics to U.S. federal agencies such as FDA. More information can be found at [www.regulations.gov](http://www.regulations.gov).

This report summarizes the input shared by patients and patient representatives during the meeting, webcast, and through the public docket. To the extent possible, the terms used in this report to describe specific experiences with organ transplantation reflect the words used by in-person, 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 related to organ transplantation that are not included in this report.

The input from the meeting and docket comments reflect the range of patients' experiences with organ transplantation. While the participants varied in the type of organ transplant, the input received was consistent and provided a rich depiction of the challenges faced as an organ transplant recipient. The input received highlighted the emotional, physical, and social burden of living with and managing transplanted organs. Several key themes emerged from this meeting:

- Participants broadly credited their transplants with having a transformative effect on their overall health, enabling them to lead longer and more fulfilling lives. Several participants expressed gratitude for the opportunity to receive transplanted organs, with one participant calling it a "second chance."
- While recognizing the benefits of their transplant, participants identified significant challenges in their post-transplant lives. Participants discussed a number of serious, chronic, and burdensome effects on their overall health that they experienced post-transplant. Participants who had not experienced these health effects described them as their biggest concerns for their future. In addition, participants provided rich insight into emotional impacts, including struggles with depression, constant anxiety about infection and the health of their organ.
- Patients acknowledged the importance of their treatments, but conveyed the burden of managing complex treatment regimens. While some participants expressed satisfaction with the effectiveness of their current regimen, others shared their difficulties with side effects and the burden of frequent monitoring, testing, and clinic visits. Participants discussed their hopes for improved treatment options throughout the meeting.
- Adherence to treatment regimens is a significant challenge for organ transplant recipients. Participants described treatment regimens as complex and strict; often requiring numerous daily medications, frequent monitoring of the health of the transplanted organ, and consistent visits to healthcare providers. Adherence is also affected by the burden of treatment side effects.

The patient input generated through this Patient-Focused Drug Development meeting and the public docket comments strengthens FDA's understanding of the impact of organ transplantation on patients and the treatments currently used to manage the possibility of organ rejection. FDA staff will carefully consider this input during the drug development process, including when advising sponsors on their drug development programs and when assessing products under review for marketing approval. For example, (Appendix 4) shows how this input may directly support our benefit-risk assessments for medical products under review. This input may also be of value to the drug development process more broadly. For example, it may be useful to drug developers as they explore treatments for more organ-specific targeted therapies, or in designing interventions that can facilitate patient adherence.

## **Topic 1: Patient perspectives on post-transplant health effects**

The first topic discussion focused on gathering perspectives on the impacts of transplant on participants' health and on daily life. Participants represented a range of pre-transplant health conditions and ages, but generally shared similar perspectives on the burden their post-transplant health effects had on their overall well-being. Participants also shared their concerns for their future health, particularly focusing on the potential for cancer and organ rejection in the future.

Five panelists (Appendix 2) provided comments to begin the dialogue. They included: a 50 year old man who received a heart transplant 22 years ago; a man who received a double lung transplant 13 years ago; a 28 year old woman who received a kidney transplant one year ago; a man who received pancreas and kidney transplants 27 years ago; and a 14 year old woman who received a kidney transplant 4 years ago.

Each panelist discussed the impact of their transplant(s) on his or her overall health. They acknowledged the positive impacts their transplants have had in improving their lives and managing their underlying health conditions. However, they also provided a vivid depiction of the challenges involved in living with and managing transplanted organs. They also discussed the physical and emotional effects that their transplants have on their well-being. In the large-group facilitated discussion that followed the panel discussion, most of the patients and caregivers in the audience indicated by a show of hands that their own experiences (or those of their loved ones) were reflected in the panelists' comments.

The facilitated discussion focused on a wide range of perspectives on the impacts of transplantation on participants' health and on their daily lives. Participants conveyed a general sense of gratitude for having received organ transplants; however, they also emphasized significant challenges in post-transplant life. As one participant commented, they have "exchang[ed] one set of problems for another." The remainder of this section summarizes participants' comments on post-transplant benefits, post-transplant health effects and the broader impact organ transplantation has on their daily lives.

### **Perspectives on Post-Transplant Benefits**

Participants broadly credited their transplants with causing transformative effects on their overall health. The most commonly discussed transplant benefits included reducing the burden of treatment regimens for underlying conditions, allowing them to participate in more activities and events, and enabling them to lead longer and more fulfilling lives. Several participants expressed gratitude for the opportunity to receive transplanted organs, with one participant stating, "each day is a gifted extension to the life that was threatened those many years ago."

Several participants focused on the benefits of being able to stop or reduce burdensome treatments for their pre-transplant condition. These include decreasing the number of daily medications, experiencing less pain and fatigue, maintaining a normal diet, and being less restricted in daily life. One participant said that after undergoing a transplant and going from taking 21 pills daily to 7 pills daily, "I have more energy. I don't have any pain." Another participant highlighted her personal experience with oxygen therapy, saying "I had spent 18 years of my life attached to an oxygen tank which was very restrictive... Having my liquid [oxygen] tanks removed from my home weeks after transplant was a highlight of my life."

Other participants provided specific examples of activities and events they were able to participate in because of their transplant. These included being able to work, go back to school, see the birth of grandchildren, and spend more quality time with family. Younger participants and parents described a return to a sense of “near-normal” daily life for their child and family. For example, one mother commented that “[the transplant] has given [her son] life... and given us [his parents] our lives back.” Another adolescent participant shared how she was able to participate in more every-day activities, crediting her transplant with making “a huge difference... I can go to school. I can have sleepovers and spend time with my friends, and I have a life.”

### **Perspectives on Post-Transplant Health Effects**

While recognizing the benefits of their transplant, participants identified significant challenges in their post-transplant lives. For some participants, the health effects they experienced were described as being manageable and tolerable. Others stated that they placed a significant burden on their overall health and well-being. In a polling question (Appendix 3, Q13), participants were asked to describe the most bothersome impacts of their organ transplantation on daily life. In response, participants discussed a number of serious and chronic effects on their overall health that they experienced post-transplant. Participants highlighted organ rejection, cancer, and infection as being the most significant of the numerous effects they had experienced. Several participants who had not directly experienced these effects described them as being their biggest worries for the future. As one participant stated, “while others may breeze out the door in the morning, I am already preoccupied with preventing rejection, infection and cancer.”

- **Cancer** – Most participants identified the risk of cancer as one of their most significant long-term health concerns, one that caused a significant amount of anxiety. Many participants had not experienced cancer themselves, but described the increased risk they faced due to their immunosuppressant regime. Participants listed several types of cancer they had either experienced or were at risk of developing. These included skin cancer, kidney cancer, and prostate cancer. Participants discussed lifestyle changes they had made to reduce the risk of skin cancer in particular, such as avoiding the sun and outdoor activities, constant application of sunscreen, and practicing good skin care. One participant shared how he no longer was able to participate in activities he had previously enjoyed, such as fishing, because of his need to “avoid the sun as much as possible.”
- **Organ rejection** – Several participants highlighted the risk of organ rejection as being another one of the most significant health risks they faced as transplant recipients. While only a few participants experienced organ rejection personally, most identified it as being one of their biggest concerns for their future health. One participant who had suffered from organ rejection described their experience as an “intense struggle.” Participants stated that options for patients who experience organ rejection and lose their graft are limited; with one participant summarizing the outcomes as “either you die or get another organ.”
- **Infection** – Participants described being more susceptible to various infections, flu, colds, and with slow recovery, and more frequent and more severe occurrences. One participant said that sicknesses which would normally last only for a day or two instead last for a week and occasionally require hospitalization.

Participants also described a number of less severe or less common health effects that they experienced because of their condition. These included:

- **Gastrointestinal (GI) Issues** – Participants shared a variety of GI issues they experienced, including nausea, diarrhea, irritable bowel syndrome, and gastro esophageal reflux disease. One participant stated that they were not fully aware of the types of GI issues that could arise after transplantation. Another said their GI symptoms were varied and unpredictable, sharing: “the constipation or the diarrhea, you never know what you’re going to have one day to the next.”
- **Fatigue** – Several participants described experiencing constant fatigue, tiring easily, or feeling a general lack of energy. One participant stated that “on the worst days... I can barely get out of bed.”
- **Hearing or Vision Problems** - Several participants stated that they had experienced either hearing loss, vision loss, or both. For participants experiencing vision loss, a few stated that they had cataracts or retinal disease post-transplant. A few participants stated that they did not expect to encounter these issues, such as one participant who said, “[what] surprised me the most is I do have a lot of trouble with my eyesight nowadays, and hearing.”
- **Restless Sleep** – A few participants described experiencing broken, restless, or mostly incomplete sleep. While participants did not identify lack of sleep as a major symptom, some did describe it as an additional burden on their overall health. As one participant put it, “inadequate sleep makes even the best days a little more challenging.”
- **Pain** – Participants mentioned residual pain from operations, joint and bone pain, migraines, and painful breathing, arthritis.
- **Cognitive Issues** – A few participants stated that they had experienced issues with staying focused and with short-term memory. One participant described a family member experiencing “a loss of short-term memory” after a transplant.
- **Other** – Other health effects mentioned by participants include diabetes, Guillain-Barre syndrome, sinus issues, hair loss, and others.

One common theme which emerged from the discussion was that participants expressed difficulty in determining which health effects are caused by their transplant, their underlying health condition, or their treatments (side effects from treatments are discussed later in this report). However, for several participants, this distinction was not important - they appeared to consider each of these as part of an overall burden on their health.

### **Overall Impacts on Daily Life**

Participants shared numerous perspectives on how their lives had changed post-transplant. The most commonly mentioned impacts on daily life included:

- **Concern for the future** – The most common impact shared by participants was a sense of anxiety and uncertainty about the future. Participants in particular focused on the potential for organ failure and rejection or the development of severe co-morbid conditions (such as cancer). Several participants expressed worry that if their organs failed or were rejected, that they might not be able to receive a retransplant. One participant stated that she was afraid to even visit her doctor “for fear of what they may find.” Another participant worried that she might not be able to have children, for fear of the pregnancy impacting her organ. Others expressed concerns



about the financial burden of long-term treatment regimens and potential need for additional future transplants.

- **Other emotional impacts** – In addition to long-term concerns about the future, participants provided rich insight into emotional impacts. These included anxiety about the threat of infection, stress caused by concern over the health of their organ, emotional impacts on family members, and struggling with depression. Participants also described psychological impacts when adjusting to the new reality of life post-transplant, for example being overly concerned about small illnesses. Several participants stated that the psychological adjustment period was especially difficult for recent transplant recipients, with one saying: “in that first year and a half, I struggled tremendously.” Another participant said that following her surgery, she had strong feelings of anxiety about whether the organ had been successfully transplanted. For some participants, the most significant emotional impacts are related to family members, such as one who shared “I have an 8-year old daughter who is slowly watching me fade and there doesn't seem to be a way to explain it to her.”
- **Burden of managing day-to-day life** – Participants described numerous lifestyle changes and impacts that resulted from their transplant. These included the burdens of their treatment regimen (such as taking numerous pills per day), maintaining fluid intake, changing their diet to maintain a healthy weight, and staying vigilant with food hygiene in order to minimize risk of infections. A few participants shared their challenges with staying properly hydrated, with one adding: “I have to drink 85 ounces of fluids daily, and this can be hard when you’re running from class to class.” Other participants described needing to be very careful around other people and in public spaces in order to reduce the risk of infection.
- **Social impacts** – Participants described receiving an organ transplant as having an “invisible disease.” For example, a few participants described experiencing a lack of understanding when requesting accommodations (e.g., a change in work requirements or a handicapped parking spot), because they don’t appear sick. In addition, one participant stated that the need to take numerous daily medications was a constant personal reminder that they were sick and not living a normal life.
- **Limitations on ability to participate in physical activities** – Some participants shared that they were less able to participate in physical activities due to reduced stamina, fatigue, or other post-transplant health effects.

## **Topic 2: Patient Perspectives on Transplant and Treatment Impacts**

The second topic discussion gathered patient perspectives on their treatment regimens. Five panelists (Appendix 2) provided comments to start the dialogue. They included: a 34 year old woman who received two double lung transplants, in 2010 and in 2013; a 43 year old man who received a liver transplant in 2005; a woman who received a heart transplant in 2006; a man who received three kidney transplants; and a woman who received two kidney transplants, one in 1983 and one in 1998. These panelists spoke about the effectiveness of their treatment regimens, their experience with immunosuppressants, the side effects they had experienced, and the impact of their treatment regimen on daily life. In the large-group facilitated discussion that followed, patients and patient representatives

also discussed their experiences with their therapies, with maintaining their transplanted organs, and with treating related health concerns following transplantation. Participants' perspectives on the benefits and downsides of their therapies, as well as what they would look for in an ideal treatment, are summarized below.

### **Perspectives on current treatments**

Participants described complex treatment regimens for managing their transplanted organs. These regimens included numerous prescription drug medications:

- Almost all participants reported (Appendix 3, Q14) use of calcineurin inhibitors (such as tacrolimus or cyclosporine) and glucocorticoids (such as prednisone) for immunosuppression. Approximately three-quarters of the participants reported using purine antagonists (such as azathioprine or mycophenolate mofetil), and approximately one-fifth reported using mammalian target of rapamycin inhibitors (such as sirolimus, everolimus). Other immunosuppressants identified by participants included belatacept or mycophenolic acid.
- Approximately two-fifths of participants reported using opioid pain medications.
- Approximately one-fifth of participants reported using antidepressant drugs (such as Elavil (amitriptyline), Prozac (duloxetine), Effexor (venlafaxine))
- Approximately half the participants reported taking other prescription medications, including antibiotics, antifungals, antivirals, cancer medications (such as chemotherapy drugs), cholesterol medications, blood pressure medication, lipid regulators, medications to treat gastrointestinal issues, pain medications, and steroids.

Participants' experiences with prescription drugs, non-drug therapies, and other types of treatments are summarized below.

#### *Prescription drugs*

Participants offered differing comments about their experiences with their post-transplant prescription drug treatments. Overall, most participants acknowledged that their treatment regimens played an important role in maintaining the health of their transplanted organ. Many participants commented that they had not experienced complications with organ rejection and considered that to be an indication of treatment success. One participant said her regimen was working "perfectly." Others stated that their treatment regimens were working adequately, and that the positive aspects of having received a transplanted organ outweighed any related treatment burden. As one participant put it, "I honestly do not think there are any downsides to the current treatment regimen. Sure, it does get difficult, annoying and frustrating ... But, reality is if I don't do it I lose a kidney." Others felt that their treatment regimens worked well at controlling symptoms, such as one participant who said their regimen "totally help[s] manage the most significant symptoms I've experienced [post] transplant." However, while most participants acknowledged the life-saving benefits of their treatments, many also emphasized the downsides they associated with their treatment regimens and the challenges they faced in finding a treatment regimen that worked for them.

#### *Treatment downsides*

When discussing their treatment regimens, participants largely focused on their immunosuppressant therapies. Participants shared a wide range of experiences and perspectives on the numerous

immunosuppressant options. Some participants expressed satisfaction with both the result of their immunosuppressant treatments, and stated they received minimal side effects. Others faced significant difficulties in finding a regimen that worked for them. Some of the challenges participants listed included: sensitivity to or intolerability of certain immunosuppressants, inability to switch treatments or find better alternatives, immunosuppressants causing conflict with other medications, needing to take other medications to handle immunosuppressant side effects, the burden of daily medications and frequent clinic visits, and underlying conditions interfering with treatment regimens. One participant shared their experience with what initially appeared to be a rejection episode, only to discover later that “it wasn’t recurrence but just not the right combination of immunosuppressants for me.” Another participant stated that he stopped taking an antidepressant due to the risk of interference with his immunosuppressants. Other participants focused on the additional risks they faced due to their immunosuppressant regimen, such as increased risk of infection, cancer, and other health effects.

In addition to the challenges some participants experienced with finding the right immunosuppressants, many participants described, in detail, the burden of side effects they experienced due to their treatments. The most commonly mentioned side effects included cancer, diabetes, tremors, weight gain, gastrointestinal issues, and organ damage. For example, one participant shared “I lost my second kidney because of mycophenolate.” Other side effects mentioned included acne, cramps, dental and bone problems, fatigue, increased blood pressure, hearing and vision loss. Several participants expressed frustration with the extent of the side effects they experienced, including one participant who stated that her treatment regimen “does not manage my symptoms, just causes them.”

#### *Clinic visits and monitoring*

In addition to discussing the benefits and side effects, several participants offered perspectives on managing their regimens, such as maintaining clinic visits, monitoring their blood levels, and adhering to their medications. Overall, participants generally found monitoring to be a useful component of a successful treatment regimen. Some participants credited their monitoring with maintaining good health, such as one participant who stated, “my current regimen seemed to be working perfectly, with semiannual clinic visits and testing, we catch issues early and treat them with minimal pain or damage.” Several participants, however, mentioned the burden of their monitoring procedures, which include needing to schedule, prepare, undergo, and pay for numerous tests, checkups, and procedures on a routine basis. As one participant said “I have spent hours scheduling, preparing for, enduring, and recovering from daily, weekly, monthly, quarterly and annual checkups, tests and horrible procedures.” Another participant shared a similar perspective, saying, “Monthly blood work to check my tacrolimus levels is annoying, and it’s worse if I get sick. Then I end up getting labs every two days until I get better.”

#### *Adherence*

FDA was particularly interested in hearing participants’ insight into challenges with medication adherence. Throughout the meeting, participants discussed their perspectives on the importance of adhering to a consistent treatment regimen, their difficulties with adherence, and their thoughts on improving adherence. Most participants recognized the role their medications have in maintaining organ health and preventing rejection. However, they described a number of challenges to adherence they faced, including the frequency and high amount of medications taken, coordinating medication with diet, the burden of clinic visits and monitoring, the impact of side effects, and remembering to take medications at the proper time. One participant described the strict requirements of their

regimen, saying “medications ... have to be taken on the spot at 12 hours ... oftentimes you have to have an empty stomach for two hours and an empty stomach for one hour afterwards ... if you make a mistake there, then it throws off the rest of your day.” Participants also shared perspectives on improving patient adherence, including reducing the number of treatments per day and improving communication of the importance of adherence, especially to pediatric transplant recipients.

### *Non-drug therapies*

In response to a polling question (Appendix 3, Q15), most participants indicated that they used non-drug therapies as part of their treatment regimen. Around three-quarters of participants indicated they had undergone diet modifications and behavioral changes (such as limiting alcohol or tobacco use). Two-thirds of participants said they incorporated exercise and other physical activities. Roughly half of participants said they used over-the-counter products (ibuprofen or naproxen) as well as dietary and herbal supplements. Some participants also indicated that they used complementary or alternative therapies (such as acupuncture or massage) and physical or occupational therapy. Several participants said they joined support groups or underwent therapy in order to help manage their anxiety and depression.

### **Perspectives on ideal treatments for organ transplantation**

Participants provided a range of perspectives on specific attributes of an ideal post-transplant treatment. Several participants identified a need for more therapies focused on long-term protection of the transplanted organ and pharmacologic therapies that do not harm the organ. Others focused on a desire for therapies with fewer long-term side effects, and fewer risks from immunosuppression (such as cancer and infection). In response to a polling question (Appendix 3, Q16) asking which factors rank as most important to participants’ decisions about using a therapy, the two most commonly selected answers were to reduce common side effects and to reduce rare but serious side effects. In addition, several participants stated that they would like to reduce the frequency of administration of the therapies (e.g., overall number of medication), such as one participant who said “my ideal treatment would be one where ... I don’t have to take as many pills, I don’t have to take them every 12 hours.” Other participants also mentioned that they would like targeted therapies, such as one participant who stated “I hope specifically for better approaches to immunosuppression that target organ specific response.” In addition to their perspectives on ideal therapies, some participants also stated that they felt the need for improved communication between healthcare professionals and patients.

## **Summary of Scientific Session**

In the afternoon, FDA continued the discussion with a scientific session to explore medication adherence and experience with intervention to mitigate nonadherence. This session was intended to provide a platform for patients, academic and industry experts, healthcare providers, government officials, and advocacy organizations, to share their perspectives and gather information on current approaches to management of transplantation. Several presentations were given by invited experts from academia. The session was split into presentation and discussion segments.

The first scientific discussion session was titled, “Causes of Late Allograft Loss and The Impact of Nonadherence, Definitions, Terms, and Background” during which four topics were presented.

- Dr. Peter Nickerson, MD from the University of Manitoba began the presentations with an overview of late allograft outcomes, touching on etiology, risk factors and natural history. Dr. Nickerson’s presentation explored the independent predictors of risk for forming antibodies against graft post-transplant. The presentation concluded with a discussion of needing to better match donors to recipients, and needing to better understand non-adherence.
- Dr. Rita Alloway, PharmD, from the University of Cincinnati College of Medicine introduced important concepts in non-adherence in solid organ transplant recipients. This presentation focused on definitions and identification, differentiating between medication nonadherence and compliance, and also looked at the detection and risk factors. Dr. Alloway concluded with an examination of the relevance of various measures of pharmaco-adherence as they apply to transplantation.
- Dr. Mary Amanda Dew, PhD, from the University of Pittsburgh School of Medicine explored the prevalence of nonadherence after organ transplantation. This presentation focused on the question of determining how common nonadherence is in order to grasp the scope of the problem. The presentation touched on two different methods, one quantitative and focusing on patient responses and biologic measures, and the other qualitative and relying on patient descriptions of their problems and how they solve them. The presentation summarized the results of a series of analyses done on existing adherence data.
- Dr. Robert Ettenger, MD, from Mattel Children's Hospital and David Geffen School of Medicine at UCLA covered adherence to immunosuppressive medications in pediatric and adolescent transplant recipients, from his view as a pediatric nephrologist. The presentation focused on the graft failure rates for adolescents, and the causes behind the failure rate - antibody-mediated rejection, likely secondary to medication nonadherence. The presentation then explored the link between donor-specific antibodies and long-term transplant outcomes and subsequent grafts.

Following these first four presentations, FDA, patient and other participants were given the opportunity to engage in dialogue with the presenters. Participants discussed the need to better communicate to the patient community the importance of taking medication, as well as the need for better communication between doctors and patients in general. One participant added that she saw a need to better engage patients in being involved in their own care. Some participants also discussed the difficulty of getting healthcare providers to discuss the impact of not following a treatment regimen exactly. Participants stated that their doctors were sometimes too focused on trying to achieve “perfect adherence,” and were often unwilling to discuss the impact of taking less than 100% of medication or taking medication at the incorrect time of day. In response to a show of hands, several participants indicated that they felt that healthcare providers were too overbearing about medication adherence, and stated in a follow-up discussion that they wished for better communication on this aspect of their treatment regimens.

The question and answer session with the speakers and patients was followed by the second scientific discussion session, titled: Interventions to Mitigate Non-Adherence, during which four additional presentations were made.

- Dr. William E. Fitzsimmons, PharmD, from Astellas Pharma Global discussed pharmaceutical dosage forms that pharmaceutical companies had developed in transplantation and other therapeutic areas to help improve adherence. The presentation touched on several different approaches, including sustained release technologies, transdermal patches, melting tablets,

long-lasting injections, chewable tablets, and fixed dose combinations. The presentation then explored the other factors adding complexity to adherence, such as dose frequency, food restrictions, and refrigeration.

- Dr. Mary Amanda Dew (University of Pittsburgh) explored interventions to maximize adherence after heart, lung, or liver transplantation in adults. The presentation focused on reviewing data and data limitations on adherence in the adult heart, lung, and liver transplant population. The presentation then addressed the topic of how to increase the effectiveness of interventions, focusing on a few methods of intervention, including electronic and face to face multicomponent (using multiple methods). The presentation concluded by stating that the area is not well understood because there are significantly fewer studies on heart, lung, or liver recipients relative to kidney recipients.
- Dr. Marie Chisholm-Burns, PharmD from the University of Tennessee College of Pharmacy & College of Medicine focused on interventions to improve adherence among adult renal transplant recipients. The presentation discussed two studies on adherence in renal transplant patients. One study explored using behavioral contracts to improve adherence, and one exploring randomly separating groups into pharmacist intervention and non-intervention. The presentation concluded by saying that while the methods used in the studies were very individualized, they did successfully improve adherence in transplant recipients.
- Dr. Robert Ettenger(UCLA) focused on interventions to improve medication adherence and outcomes in adolescent transplant recipients. The presentation started off by discussing what a successful intervention entails and difficulties with adolescents when it comes to adherence (difficulties such as adolescents not feeling any pain from missed medications, and not considering the future). The presentation then touched on the importance of educational interventions while also stating that education alone is insufficient to improve adherence. The presentation then touched on multicomponent adherence, saying that it probably has the highest effectiveness, although all interventions are strongest immediately after intervention and fade over time.

A panel discussion followed these presentations, addressing topics related to adherence and transplant patients. Topics discussed included: thoughts on making regimens easier to follow, understanding the patient community, patient established support groups, utilizing social media, increasing patient involvement in clinical trials, and other methods of improving adherence through communication and patient community outreach and engagement. Participants restated their desire for treatment regimens with fewer daily medications. Others emphasized the importance of promoting and facilitating communication between experienced transplant recipients and newer recipients in order to improve adherence. Some addressed the importance of care centers, social media, and social groups, including one participant who stated that “social media and support groups have really held me to a certain level of accountability.” Others focused on reducing the impact of medication on daily life and on patients’ psyches, stating that the constant need to take medications creates a negative stigma for patients, emphasizing that they are sick.

## Conclusion

Organ transplantation is a life-altering experience, with physical, emotional and social impacts. New approaches are needed to improve the long-term success of transplanted organs, to prevent and treat antibody-mediated rejection, to individualize treatment, and to reduce the adverse reactions associated with immunosuppressant regimens. Patient perspectives play an important role when considering how to best facilitate drug development post-organ transplantation. These perspectives also inform how patients view the benefits and risks of various drug products in the complex area of post-transplant treatment.

The perspectives shared by participants at this meeting provided a vivid examination of the challenges and burdens facing patients who have received an organ transplant. FDA is grateful to all the participants for attending the meeting and sharing their perspectives. This Patient-Focused Drug Development meeting on organ transplantation provided FDA the opportunity to hear from patients and caregivers first-hand the impact of organ transplantation and post-transplant treatment regimens on patients' lives. FDA recognizes that patients have a unique ability to contribute to our understanding of their condition and treatment management, which is important to our role, and that of others, in the drug development process.

FDA is grateful to the patients and caregivers who thoughtfully and bravely provided such personal insight into their lives. Through this meeting, FDA learned more about what matters most to patients and caregivers regarding the impact of organ transplantation and post-transplant treatment. FDA shares the patient community's desire and commitment to advancing the development of safe and effective treatment options for managing post-transplant care.

## Appendix 1: Meeting Agenda

### Public Meeting on Patient-Focused Drug Development for Patients Who Have Received an Organ Transplant

September 27, 2016

- 8:00 – 9:00 am      **Registration**
- 9:00 – 9:05 am      **Welcome**
- Meghana Chalasani
- Office of Strategic Programs (OSP), Center for Drug Evaluation and Research (CDER), FDA*
- 9:05 – 9:10 am      **Opening Remarks**
- Edward M. Cox, MD, MPH
- Director, Office of Antimicrobial Products (OAP), CDER, FDA*
- 9:10 – 9:20 am      **Overview of FDA’s Patient-Focused Drug Development (PFDD) Initiative**
- Theresa Mullin, PhD
- Director, OSP, CDER, FDA*
- 9:20 – 9:30 am      **An Overview of Organ Transplants and Available Post-Transplant Treatment Options**
- Marc Cavaillé-Coll, MD, PhD
- Medical Officer, Division of Transplant and Ophthalmology Products (DTOP), OAP, OND, CDER, FDA*
- 9:30 – 9:35 am      **The Road from PFDD Meetings to Clinical Trial Endpoints**
- Michelle Campbell, PhD
- Clinical Outcomes Assessment (COA) Staff, Office of New Drugs, CDER, FDA*
- 9:35 – 9:45 am      **Overview of Discussion Format**
- Sara Eggers, PhD
- OSP, CDER, FDA*
- 9:45 – 10:15 am      **Panel #1 Discussion on Topic 1**
- A panel of patients will provide comments to set up the context on life after receiving an organ transplant
- 10:15 – 10:45 am      **Large-Group Facilitated Discussion on Topic 1**
- Patients and patient representatives in the audience are invited to add to the dialogue



10:45 – 11:00      **Break**

11:00 – 11:30      **Panel #2 Discussion on Topic 2**

A panel of patients will provide perspectives on managing their condition.

11:30 – 12:30      **Large-Group Facilitated Discussion on Topic 2**

Patients and patient representatives in the audience are invited to add to the dialogue.

12:30 – 1:15 pm      **Lunch**

### **Afternoon Scientific Session: Medication Adherence and Experience with Intervention**

1:15-1:20 pm      **Afternoon Opening Remarks**

Ozlem Belen, MD, MPH

*Deputy Director for Safety, DTOP, OAP, OND, CDER, FDA*

#### **Scientific Discussion #1: Causes of Late Allograft Loss and The Impact of Nonadherence,**

##### **Definitions, Terms, and Background**

1:20-1:35 pm      **Overview of Late Allograft Outcomes: Etiology, Risk Factors and Natural History**

Peter Nickerson, MD, FRCPC, FCAHS

*Vice-Dean (Research) and Distinguished Professor, Flynn Family Chair in Renal Transplantation,*

*Rady Faculty of Health Sciences, University of Manitoba*

1:35 – 1:50 pm      **Exploring Non-Adherence in Solid Organ Transplant Recipients**

Rita Alloway, PharmD, FCCP

*Research Professor of Medicine & Director, Transplant Clinical Research,*

*University of Cincinnati, College of Medicine*

1:50 – 2:05 pm      **Prevalence of Nonadherence after Organ Transplantation**

Mary Amanda Dew, PhD

*Professor of Psychiatry, Psychology, Epidemiology, Biostatistics, and Clinical and Translational Science,*

*Director, Clinical Epidemiology Program, Western Psychiatric Institute and Clinic*

*University of Pittsburgh School of Medicine*

2:05 – 2:15 pm **Adherence to Immunosuppressive Medications in Pediatric and Adolescent Transplant Recipients: A Pediatric Nephrologist's View**

Robert Ettenger, MD

*Distinguished Research Professor, Emeritus, Department of Pediatrics, Division of Nephrology*

*Mattel Children's Hospital, David Geffen School of Medicine at UCLA*

2:15 – 2:50 pm **Panel Discussion on Session #1**

2:50 – 3:05 pm **Break**

**Scientific Discussion Session 2: Interventions to Mitigate Non-Adherence**

3:05– 3:20 pm **Pharmaceutical Dosage Forms to Improve Adherence: What Can be Done? What are the Limitations?**

William E. Fitzsimmons PharmD, MS

*Executive Vice President, Regulatory Affairs, Astellas Pharma Global*

3:20-3:35 pm **Interventions to Maximize Adherence after Heart, Lung, or Liver Transplantation in Adults**

Mary Amanda Dew, PhD

*Professor of Psychiatry, Psychology, Epidemiology, Biostatistics, and Clinical and Translational Science,*

*Director, Clinical Epidemiology Program, Western Psychiatric Institute and Clinic*

*University of Pittsburgh School of Medicine*

3:35 – 3:50 pm **Interventions to Improve Adherence Among Adult Renal Transplant Recipients**

Marie Chisholm-Burns, PharmD, MPH, MBA, FCCP, FASHP, FAST

*Dean and Professor, College of Pharmacy, Professor of Surgery, College of Medicine, University of Tennessee*

3:50 - 4:00 pm **Interventions to Improve Medication Adherence and Outcomes in Adolescent Transplant Recipients**

Robert Ettenger, MD

*Distinguished Research Professor, Emeritus, Department of Pediatrics, Division of Nephrology*

*Mattel Children's Hospital, David Geffen School of Medicine at UCLA*

4:00 – 4:35 pm **Panel Discussion on Session #2**

4:35 – 4:50 pm      **Open Public Comment**

4:50 – 5:00 pm      **Closing Remarks**

Renata Albrecht, MD

*Director, DTOP, OAP, OND, CDER, FDA*

### **Discussion Questions (Morning Session):**

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

1. What have been the most significant changes in your overall health since you received your transplanted organ?
  - a) How long has it been since you received your transplant?
2. Focusing on symptoms related to your organ transplant and post-transplant effects, which 1-3 symptoms have the most significant impact on your life? (Examples may include pain, infection, anxiety, etc.)
3. 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 transplant? (Examples of activities may include sleeping through the night, driving, walking/running, exercising, etc.)
  - a) How do your symptoms and their negative impacts affect your daily life on the best days? On the worst days? (Examples may include limitations on the ability to undertake physically strenuous activities, restrictions on the ability to travel, lack of appetite, fatigue, etc.)
4. How has your experience with your transplanted organ changed over time? Do particular symptoms come and go as your duration of time with a transplanted organ has increased? If so, do you know of anything that makes your symptoms better? Worse?
5. What worries you most about your health post-transplant?

#### Topic 2: Patients' perspectives on transplant and treatment impacts

1. What are you currently doing to maintain your transplanted organ or treat related health concerns following transplantation? (Examples may include immunosuppressants, antibiotics, antivirals, over-the-counter products, and other therapies including non-drug therapies)
  - a) How has your post-transplant treatment regimen changed over time, and why?
2. How well does your current treatment regimen manage the most significant symptoms you experience post-transplantation?
  - a) How well do these treatments improve your ability to do specific activities that are important to you in your daily life?
  - b) How well have these treatments worked for you as your experiences post-transplant have changed over time?
3. 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, need for multiple medications, risk of infection, need for hospitalization, etc.)
  - a) What are the biggest challenges you face in maintaining your post-transplant treatment regimen (Examples of challenges may be bothersome side effects, need for multiple medications, etc.)
4. What specific things would you look for in an ideal treatment for managing your transplanted organ?

### **Scientific Discussion Questions (Afternoon Session):**

#### Panel 1 Questions:

1. How well do we understand the extent of non-adherence in patients post-transplantation? What type of non-adherence is affecting patient outcomes the most?
2. Are healthcare providers appropriately involved when it comes to promoting adherence or are they not paying enough attention? What improvements would you suggest?

3. How critical is it to collect adherence data in clinical trials of new drugs or new regimens? What are the consequences of not doing so?

Panel 2. Questions:

1. How can we incentivize (or promote) adherence?
  - a. Does one strategy work for all patients or is there a personalized way to incentivize adherence?
  - b. Would electronic monitoring help? Would keeping track of e.g., tacrolimus or cyclosporine trough concentrations help?
2. What are some barriers to increasing transplant programmatic resources allocated to promoting adherence efforts?
3. How can transplant programs help patients to support each other in their efforts to adhere to their medical regimen after transplant?
4. What medication reminder systems are most acceptable and helpful to patients?
  - a. What are the challenges to using them? How can we track the usefulness or success of these systems?
  - b. How can we harness power of “gamification” (use of game design) and health apps to support patients’ ability to track their medication taking and other medical regimen requirements?
5. What is preventing the development of more “forgiving” drugs so it would be less critical if patients miss a dose

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

### **Patient Panel, Topic 1**

- Lindsey Duquette
- Jim Gleason
- Jeffrey Goldstein
- Michael Garrett
- Leilah Sampson

### **Patient Panel, Topic 2**

- Piper Beatty
- Dan Bonner
- Deborah Heffernan
- Jack Lennon
- Roberta Wager

### **FDA Panel**

- Renata Albrecht, Division of Transplant and Ophthalmology Products (DTOP), Center for Drug Evaluation and Research (CDER)
- Ozlem Belen, DTOP, CDER
- Michelle Campbell, Office of New Drugs, CDER
- Marc Cavaillé-Coll, DTOP, CDER
- Edward Cox, Office of Antimicrobial Products, CDER
- Arturo Hernandez, Division of Reproductive, Gastro, Renal, and Urological Devices, Center for Devices and Radiological Health
- Theresa Mullin, Office of Strategic Programs, CDER
- Ergun Velidedeoglu, DTOP, CDER

## Appendix 3: Meeting Polling Questions

### Demographic Questions

1. Where do you live?
  - a. Within Washington, D.C. metropolitan area (including the Virginia and Maryland suburbs)
  - b. Outside of the Washington, D.C. metropolitan area
  
2. Have you received an organ transplant?
  - a. Yes
  - b. No

*We will ask that the remainder of the questions be answered by participants who responded “yes” to Question 2, or by a caregiver answering on behalf of an organ transplantation recipient.*

3. What is you or your loved ones age?
  - a. < 1
  - b. 1-10
  - c. 11-17
  - d. 18-34
  - e. 35-49
  - f. 50-64
  - g. 65+
  
4. Do you identify as:
  - a. Male
  - b. Female
  
5. What type of organ transplant have you received?
  - a. Kidney
  - b. Heart
  - c. Liver
  - d. Lung
  - e. Pancreas
  - f. Multiple different organs
  - g. Others not mentioned

6. What is the length of time since you received an organ transplant?

- a. Less than 1 year ago
  - b. 1-2 years ago
  - c. 3-5 years ago
  - d. 6-10 years ago
  - e. Greater than 10 years ago
7. Have you received more than one organ transplant (or retransplant)?
- a. Yes
  - b. No
8. Did you receive your organ transplant from a living or deceased donor? **Check all that apply.**
- a. Living donor
  - b. Deceased donor
  - c. I don't know
9. Have you experienced organ rejection?
- a. Yes
  - b. No

#### Question for Topic 1

10. What comorbid condition(s) have you experienced post-transplantation (if applicable)? **Check all that apply.**
- a. Bacterial ( such as urinary tract infection, respiratory infection) or viral infection (such as cytomegalovirus(CMV), Epstein-Barr Virus (EBV), BK virus)
  - b. Cancer
  - c. Cardiovascular Disease (such as high blood pressure, coronary artery disease, heart failure)
  - d. Depression or anxiety
  - e. Diabetes
  - f. Fungal (such as candidiasis, aspergillosis) or parasitic infection
  - g. Kidney disease
  - h. Other comorbid condition(s) not mentioned
  - i. I do not have any comorbid conditions that I am aware of
11. Based on your response previously, which statement best categorizes the source of the comorbidity you experience? **Check all that apply.**
- a. The comorbidity I experienced was transmitted from the donor of my organ transplant (i.e donor-derived).
  - b. The comorbidity I experienced was present prior to my organ transplantation (i.e recipient-derived).

- c. The comorbidity I experienced was acquired in a community setting due to immunosuppression or infection.
- d. The comorbidity I experienced was acquired as an adverse effect of my post transplantation therapy regimen.
- e. Other areas not mentioned

**12. Post-transplantation, which aspects of your personal care have changed most significantly?  
Check all that apply.**

- a. Skin Care (such as reduced exposure to light, risk of cancer )
- b. Hair Care (due hair loss, increased hair growth)
- c. Dental Care (such as tooth or gum pain)
- d. Eye Care (such as vision changes, cataracts)
- e. Dietary Needs (due to constipation, diarrhea, or weight gain/loss)
- f. Other areas not mentioned

**13. What are the most bothersome impacts of your organ transplantation on your daily life? Please choose up to three impacts.**

- a. Ability to participate in or perform activities (such as work, participation in sports or social activities, driving, make or keep plans for activities, etc.)
- b. Ability to fall asleep or sleep through the night
- c. Ability to travel (such as use of public transportation, personal vehicles or commercial flights)
- d. Ability to concentrate or stay focused
- e. Ability to care for self, family, and others
- f. Impacts on sexual intimacy
- g. Impacts on social relationships
- h. Emotional impacts (such as fear, hopelessness, etc.)
- i. Other impacts not mentioned

## Questions for Topic 2

**14. Have you ever used any of the following drug therapies to manage your organ transplantation? Check all that apply.**

- a. Calcineurin Inhibitors (such as tacrolimus or cyclosporine)
- b. Glucocorticoids (such as prednisone)
- c. Purine antagonist (such as azathioprine or mycophenolate mofetil)
- d. Mammalian target of rapamycin inhibitors (such as sirolimus, everolimus)
- e. Antidepressant drugs (such as Elavil (amitriptyline), Prozac (duloxetine), Effexor (venlafaxine))
- f. Opioid pain medicines



- g. Other drug therapies not mentioned
- h. I'm not taking any drug therapies

**15.** Besides the therapies mentioned previously, what else are you doing to manage any symptoms you have experienced because of your organ transplantation? **Check all that apply.**

- a. Dietary and herbal supplements
- b. Diet modifications and behavioral changes (such as limiting alcohol or tobacco use)
- c. Complementary or alternative therapies (such as acupuncture or massage)
- d. Physical or occupational therapy
- e. Exercise and other physical activities
- f. Over-the-counter products (such as ibuprofen or naproxen)
- g. Other therapies not mentioned
- h. I am not doing or taking any therapies to treat symptoms

**16.** In addition to preventing organ rejection, of the following factors, which two would you rank as most important to your decisions about using a therapy to manage your organ transplantation? **Please choose two.**

- a. The frequency of administration of the drug (i.e twice a day or once a day)
- b. The common side effects of the treatment (such as nausea, fatigue, and weight gain)
- c. The possibility of rare, but serious side effects (such as nerve and liver damage)
- d. The possibility of interactions with medications for other comorbidities (such as hypertension or diabetes)
- e. Your access to this treatment (for example, insurance coverage)
- f. Other considerations

## Appendix 4: Incorporating Patient Input into a Benefit-Risk Assessment Framework for Organ Transplantation

### 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<sup>3</sup>. The Benefit-Risk Assessment Framework involves assessing five key decision factors: *Analysis of Condition*, *Current Treatment Options*, *Benefit*, *Risk*, and *Risk Management*. When completed for a particular product, the Framework provides a succinct summary of each decision factor and explains FDA's rationale for its regulatory decision.

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

The input provided by patients and patient representatives through the Patient-Focused Drug Development Public Meeting on Patients Who Have Received an Organ Transplant 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 organ transplantation below draws from various sources, including what was discussed at the Patient-Focused Drug Development Public Meeting on Patients Who Have Received an Organ Transplant on September 27, 2016. This sample framework contains the kind of information that we anticipate could be included in a framework completed for a drug under review for organ transplantation. 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.

---

<sup>3</sup> 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>.

Dimensions	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<ul style="list-style-type: none"> <li>- In 2015, over 25,000 people in the United States received an organ transplant.</li> <li>- The types of organs transplanted annually in the United States include kidney, liver, pancreas and intestine, as well as heart, lung and heart/lung.</li> <li>- Although infrequent, infectious pathogens (i.e., viruses, bacteria, fungi, or protozoa/parasites) have been unknowingly transmitted through transplants.</li> <li>- Laboratory testing for certain infectious pathogens is required in deceased organ and tissue donors and living kidney donors</li> <li>- <i>See the Voice of the Patient report for a more detailed narrative.</i></li> </ul>	<p>Organ donation and transplantation to treat end-stage organ disease can be lifesaving and transformative for patients with a serious condition. Serious illness, graft loss and death can also occur from undetected infections in donor organs and tissues.</p>
Current Treatment Options	<ul style="list-style-type: none"> <li>- Organ transplantation requires pharmacologic and non-pharmacologic management before and after receipt. Post-transplant management typically addresses four main objectives: prevention of organ rejection, treatment of the underlying medical condition, treatment of emergent complications of the immunosuppression regimen, and prevention and treatment of infections.</li> <li>Medications to prevent and treat rejection include induction immunosuppression with intensive combination regimens, maintenance immunosuppression with less intensive combination regimens, and additional medications for treatment of acute rejection.</li> <li>- Other treatments include medications to prevent and treat viral, bacterial, fungal and other opportunistic infections; medications for treating the underlying medical conditions that led to the organ failure (such as hypertension, diabetes, and hepatitis C); and medications that treat the emerging complications, including hypertension and new onset of diabetes.</li> <li>- Medication adherence is a challenge in maintaining a successful treatment regimen.</li> <li>- <i>See the Voice of the Patient report for a more detailed narrative.</i></li> </ul>	<p>New approaches are needed to improve the long-term success of transplanted organs, to prevent and treat antibody-mediated rejection, to individualize treatment, and to reduce the adverse reactions associated with immunosuppressant regimens.</p> <p>In addition, new approaches are needed to help improve medication adherence.</p>