

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

Chagas Disease

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Center for Drug Evaluation and Research (CDER)
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Introduction

On April 28, 2015, FDA held a public meeting to hear perspectives from people with Chagas disease about their condition, its impact on their daily life, and their perspectives on approaches to treating Chagas disease. 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>

In the afternoon of April 28, FDA held a scientific workshop to explore scientific challenges involved in clinical development of drug products intended to treat Chagas disease. This workshop was intended to provide information for and gather perspectives from various stakeholders in the drug development process, including patients, patient advocacy organizations, health care providers, academic experts, and industry. A brief summary of the scientific workshop is included near the end of this report.

Overview of Chagas Disease

Chagas disease is spread by contact with feces of an infected insect (triatomine) carrying the agent of the disease, a parasite called *Trypanosoma cruzi*. This parasitic disease is estimated to affect around 6-7 million people worldwide, primarily in rural areas in Latin America. While more common in South America, it has previously been less common in North America. Currently in the United States, the disease is estimated to affect more than 300,000 people, most of whom acquired the disease in foreign countries. There are two phases of Chagas disease: the acute phase and the chronic phase. The acute phase is often asymptomatic and can last a few weeks or months after infection. Only rarely do infected persons experience life-threatening disease in the days to weeks after they are infected (early or acute phase). The infection persists for years without any symptoms, and some patients may develop serious heart problems or gastrointestinal tract problems years or decades after they have been infected. The lack of early diagnosis and treatment is critical to eradicate this disease.

Certain people are at higher risk of the more serious form of the disease. Primarily, this includes people with weakened immune systems, such as patients with HIV/AIDS or those undergoing treatment after an organ transplant. The disease can also be spread from mother to child (congenitally), via organ transplant, or via blood transfusion. Less common forms of transmission include laboratory accidents and contaminated food or drink. The disease is not spread through casual person to person contact.

In general, infections last for life if treatment is not administered. There are no treatments currently approved by the FDA; however, two drugs (benznidazole and nifurtimox oral tablets) are available through the Centers for Disease Control and Prevention (CDC) at a physician's request.¹ These treatments are primarily targeted to patients (of any age) with acute Chagas disease or for patients up to age 50 years with chronic Chagas disease. Patients living with chronic Chagas disease often require

¹ For more information, see the CDC's Drug Service website:

<http://www.cdc.gov/laboratory/drugservice/index.html>

additional treatments focused on managing long-term effects of the disease, such as gastrointestinal problems or heart failure.

Meeting and Report Overview

This meeting provided FDA the opportunity to hear directly from patients, advocates, healthcare professionals, and academic researchers about their perspectives on Chagas disease and its treatments. The morning discussion focused on two key topics: (1) disease symptoms and daily impacts that matter most to patients, and (2) patients' perspectives on current approaches to treating Chagas disease. The questions for the morning discussion (Appendix 1) were published in a [Federal Register Notice](#) that announced the meeting. A panel of 4 patients and 1 advocate shared their experiences on symptoms and impacts of Chagas disease on their daily life. This panel also provided comments on their treatment regimens and how they make decisions regarding treatments. Panel comments were followed by a facilitated discussion inviting comments from other meeting participants. 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 invited to submit comments throughout the discussion. FDA also opened a [Public Docket](#)², which was open until June 29, 2015. FDA received one docket comment, submitted by the Chagas Disease Alliance. These comments were reflective of what was heard during the meeting.

More information on the meeting, including the archived webcast recording and meeting transcript, is available on the meeting website: <http://www.fda.gov/Drugs/NewsEvents/ucm420130.htm>.

This report summarizes the input provided by the patient panelists, representatives, and healthcare professionals during the morning Patient-Focused Drug Development meeting. It also includes a brief overview of the discussion during the afternoon's scientific workshop. To the extent possible, the terms used in this report to describe specific symptoms and treatment experiences reflect the words used by in-person participants and web participants. 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 Chagas disease that are not included in the report.

The input generated by this discussion highlighted the many ways in which Chagas disease impacts patients' lives. These include:

- Participants emphasized and provided great detail on the significant **lack of awareness** and understanding of Chagas disease in the healthcare community. They provided examples of the challenges they faced with the disease due to the lack of awareness, including the lengthy and often confusing process of establishing a diagnosis. They also discussed issues related to clinical trials for Chagas disease.
- The **uncertainty** that patients live with during the asymptomatic and symptomatic phases of the disease. While some participants had few physical symptoms, others had more significant complications, such as serious cardiac issues.

² 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. Comments submitted to the docket can be found online and are not summarized here.

- The significant **emotional toll** the disease takes on patients' lives. Participants identified struggling with fear of future symptoms, social isolation, difficulty in finding others to discuss their experiences with, and the frustration of living with a condition that was not well understood.
- The **burden of treatment** options. Participants described frequent doctor visits to monitor their health for the onset or worsening of symptoms, as well as the difficulties they experienced in gaining access to treatments. Participants with significant physical symptoms (such as heart failure) also noted burdensome side effects of surgical procedures and drug treatments.

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

The Patient-Focused Drug Development meeting began with 4 patient panelists and 1 patient representative who provided comments on their experiences with the symptoms of Chagas disease.³ The panelists are described below:

- Carlos⁴, who emigrated to the United States from El Salvador, was diagnosed 4 years ago after living with the disease for much of his life. Carlos recalled a memory of insects that would come “during the night” and bite. He shared that he “suffered from this for a long time,” but did not know of Chagas disease.
- Maria, who emigrated to the United States from Honduras, contracted Chagas during her childhood. Maria noted that as a child, she frequently noticed insects in her home, but never imagined that “this little insect could cause such problems and damage.”
- Maira, who emigrated to the United States from El Salvador, learned that she had Chagas disease after donating blood to the American Red Cross in 1997. She shared that she had no memory of being bitten.
- Candace, who has lived in the United States her whole life, was diagnosed with Chagas disease a year and a half ago after donating blood. She shared that she had seen a “kissing bug” in Texas, and believed that she was infected through an open wound on her leg.
- Rachel, a physician and patient advocate at the Latin American Society for Chagas disease (LASOCHA), spoke on behalf of the LASOCHA patient population.

The patient panelists shared how their lives have been impacted since their diagnosis with Chagas disease. They shared personal experiences of the physical and emotional burden of the disease, and in particular, emphasized the difficulty they experienced in getting properly diagnosed. The panelists represented a range of symptoms and severity: from Carlos and Maria, who have experienced life-

³ Carlos' comments were interpreted and translated into English by Rachel Marcus. Maria's comments were interpreted and translated into English by a translation services representative.

⁴ Previous Voice of the Patient reports have focused on summarizing the input from the audience at large, rather than any specific individual's comments. However, all four patients attending the Chagas meeting served on the patient panel, and the morning discussion explored each individual's comments in detail. As a result, this report will identify to each panelist by name when referring to their comments.

threatening symptoms, to Maira and Candace, who currently experience few symptoms. In general, their comments were echoed by healthcare professionals and patient advocates who spoke at the meeting about the wider Chagas patient population. Each patient's comments are summarized in more detail below.

Patients Experiencing Significant Symptoms

Carlos shared his perspective as a Chagas patient who has experienced life-threatening cardiac issues, specifically heart disease, and other significant symptoms as a result of his disease. Carlos described his initial symptoms of dizziness, vomiting, and loss of appetite, which became significantly worse over time. He shared that severe congestive heart failure led to a 5-month hospitalization and surgery to implant a ventricular assist device. During that time, he began to experience headaches and felt the emotional burden of his condition: "You don't want to talk to anybody and you are just so sad." In addition to his cardiac issues, Carlos described suffering from a number of symptoms, including: weight fluctuations, body aches, coughing, and difficulty with restful sleep. Carlos described how some of his symptoms exacerbated others. For example, he described how vomiting, which was one of the most significant symptoms he experienced, often resulted in coughing fits. Coughing, fear, and anxiety began to interfere with being able to sleep. He also stated that he occasionally had other symptoms or worsening symptoms when he missed his treatments.

Maria noted that her initial symptoms included cough and cold symptoms, which at first were misdiagnosed as a common cold. However, her symptoms did not improve. As her cough became more severe, she felt "very fatigued and tired", and she started having body pains, dizziness and chills. Similar to Carlos, Maria described suffering from heart failure due to her Chagas disease. As her cardiac issues worsened, Maria described experiencing difficulty breathing and walking. Maria shared that she received a heart transplant due to the progression and severity of her heart failure.

Patients Experiencing Few or No Physical Symptoms

Maira and Candace both provided their perspectives of living with Chagas disease, so far experiencing few or no physical symptoms of the disease. Maira described the emotional "roller coaster ride" of living with Chagas disease, noting her own and the medical community's lack of understanding of Chagas disease. She noted that although she does not have any physical symptoms, she feels frustrated and worried about future symptoms that she "can't see" just yet, sharing "I think by the time we get to a symptom, it's probably too late, if something has already happened." She shared that her risk of "having a heart attack at any given moment" has caused her significant emotional distress.

Candace provided a similar perspective to Maira. She shared that she was unable to know for sure whether the symptoms she experiences are directly linked to Chagas disease, or if they resulted from her anxiety due to having the disease. For example, she shared, "If my chest is hurting me, is it because I have some little critter crawling around in me? I don't know. I think a lot of that is anxiety." Candace also identified difficulties with sleep, including insomnia and unrefreshing sleep sharing, "I wake up five and six times a night and then go right back to sleep." She noted that her lack of energy made it difficult for her to participate in physical activities such as walking, caring for her household, or interacting with her grandchildren. Similar to other panelists, Candace reiterated that her biggest worry was not knowing what the future with Chagas disease will hold: for example, what cardiac symptoms might arise and how she would manage her condition. Candace also shared that she has felt shame and embarrassment because of her diagnosis, and that she felt socially isolated to not be able to discuss her diagnosis with others.

Comments from other meeting participants

The comments by healthcare professionals and other participants echoed the panelists' perspectives on the burden of Chagas disease, especially regarding the general lack of awareness on Chagas disease in the medical community in the United States. Several healthcare professionals emphasized that patients who may not have physical symptoms experience daily worry of how and when their future symptoms will manifest. For example, Rachel reiterated that many patients experienced "profound fear" of the future, and that many often felt that they were faced with a "doom diagnosis." Rachel indicated that for other patients who have advanced cardiac issues due to Chagas disease, the burden of treatment was also significant.

Topic 2: Patient Perspectives on Treatments for Chagas

The second discussion topic focused on patients' experiences with therapies used to treat Chagas disease and its complications. Carlos, Maria, Maira, and Candace provided comments on their experiences with drug therapies, surgical procedures, and medical devices. They also focused on other important aspects of treatments, including: adverse impacts and limitations, issues with access to treatments, issues with the process of disease diagnosis and reporting, perspectives on clinical trials, and what they would look for in an ideal treatment. Healthcare professionals in the meeting reinforced these perspectives. Panelists' perspectives on their treatments are summarized below.

Benznidazole and Nifurtimox

Two panelists shared their experiences with two medications used to treat their Chagas disease: benznidazole and nifurtimox. Although neither drug is approved by the FDA, the medications are available in oral tablets through the CDC by a physician's request.

Candace began the dialogue by sharing that she took benznidazole for over 2 months, and that she "zoomed right through it." Although Candace said that she did very well on the medication, she did share several downsides to taking the medication. She specifically noted the burden of accessing her treatment, saying that in addition to weekly blood work, "I was having to travel an hour and a half every two weeks to go and get my medication because CDC would not allow [my doctor] to give me 60 days' worth of medication." Candace commented that due to lack of any physical symptoms, "I have not taken any other medications at this time because we don't know what to look for."

Maira shared that after diagnosis, she began nifurtimox treatment. She noted that the only side effect she experienced was losing 25 pounds during therapy. Maira shared that after completing nifurtimox, the CDC recommended benznidazole treatment. However, Maira commented that she had been waiting for the benznidazole for over a year and half because of a drug shortage, and commented that she had researched purchasing the medication online. She shared that she expected the downsides of benznidazole to be similar to what she experienced on nifurtimox, sharing "[the medications] kill the bad, but they also kill the good. Unfortunately, that's the only option we have."

Healthcare professionals in the meeting also noted the burden of treatment administration and dosing of these "potent drugs." In one example, Rachel commented that treatment side effects including, headache, weight loss, and rashes can be very bothersome and can make it difficult for patients to comply with treatment. Another healthcare professional shared that some patients cannot tolerate certain side effects of nifurtimox, and although dosing can be adjusted, some have a "horrific reaction to

it.” These healthcare professionals noted the urgency and importance of having additional treatments available. They also stressed the benefits and effectiveness of current treatments in children and recently infected patients.

Treatments for Chagas-related Cardiac Issues

Maria and Carlos described how their lives have been significantly affected by their experience with heart failure and the treatments they have undergone to manage their condition. Maria noted that due to advanced heart failure, she received a heart transplant in 2014 and had a pacemaker installed. She shared that she takes a “long list of medications” to manage her condition. She specifically mentioned that she experienced intolerable adverse effects of sirolimus (an FDA approved drug marketed under the trade name, Rapamune), and had to change to another medication. Maira also shared that she undergoes annual echocardiograms and MRIs to detect potential cardiac issues.

Carlos shared his experiences with treating his Class IV congestive heart failure, which resulted from advanced Chagas disease. Carlos described requiring five month hospitalization and the placement of a pump into his left ventricle, for which he wears a bag on his chest. Carlos described a reduction in some symptoms (such as vomiting and weight fluctuations) after this procedure, saying, “With this apparatus, I feel so much better.” However, Carlos shared the cumbersome nature of the device and the limitations it has placed on his life, including being, “permanently connected to this battery.” He described having to change the pump battery every two and half hours, and having to sleep with the device plugged into a wall. He shared that he takes several medications due to the device. He noted that he has to go to the hospital for blood testing every two weeks in addition to seeing the doctor every month. Rachel added that Carlos experiences an ongoing risk of blood clotting, infection, and device failure, and that the pump was the best treatment option while he waits for a heart transplant.

Healthcare professionals said that these comments were representative of other patients with cardiac issues related to Chagas disease. One healthcare professional noted that many patients require additional medications and support for their cardiac issues (such as ventricular arrhythmias), and that by the time the patient has been seen by a physician, their condition has worsened. The healthcare professionals also noted the risks and limitations of surgical intervention, including possible rejection of the transplant, life-long medications and monitoring, and the risk of reactivating the Chagas disease. They stressed the importance of proper and quick diagnosis, so that treatments could be administered sooner, which could be more effective. This was further emphasized by one web participant from Argentina, who shared that her father was originally misdiagnosed as having congenital cardiomyopathy. He suffered a stroke and heart failure before being properly evaluated; her father was later given a pacemaker to address the cardiac issues resulting from his Chagas disease.

Other Issues Regarding Treatment of Chagas Disease

Although the meeting topics focused on the impacts and treatments of Chagas disease, meeting participants discussed a number of other issues that are important to consider when addressing the overall management of Chagas disease. These issues are briefly described below.

Issues with Diagnosis and Lack of Awareness

All panelists and participating healthcare professionals identified that the lack of awareness of Chagas disease in the healthcare community was a major issue. Several of the panelists shared similar comments on their early doctor visits:

- “[My doctor] did not know how to treat it.”
- “She [healthcare professional] couldn't answer [my questions on Chagas] because she had no idea.”
- “She [primary care physician] didn't know what to do with me. She didn't know where to send me.”
- “The one and only time they [physicians] will hear about it in their medical training is in medical school.”

Candace and Maira both described their difficulties in finding doctors familiar with Chagas disease, sharing “no one has ever heard of it.” Both mentioned that they had to see several doctors before they finally found one who was familiar with the condition. Maira shared that it took her 11 years to before she started the necessary treatments. Healthcare professionals in the room reiterated this lack of awareness among the medical community and the critical need for providing better information to newly diagnosed patients. One healthcare professional noted that the physicians with the most experience treating Chagas patients in the United States were cardiologists, not doctors specialized in treating Chagas disease. She commented, “This is not a cardiology disease. We do not want this to be a cardiology disease... we are pushing it [this message] into the primary care system...and pediatricians.”

Some meeting discussion focused on the current state of screening and diagnosis in the U.S. FDA asked healthcare professionals in the room for clarification on how Chagas disease is tracked and reported in the United States. A CDC representative noted that although Chagas disease is a reportable condition in some states, it is not a nationally notifiable disease.⁵

Healthcare professionals also called the current diagnostic system insufficient, saying that more active screening for Chagas disease beyond occasional blood or organ donation screening tests was critical. They also reemphasized the need for early diagnosis and treatment, specifically focusing on the importance of routine screening to enable treatment as early as possible after infection. A few healthcare professionals commented that their clinics provide screening for Chagas disease as a routine practice, especially for Latin American immigrant patients. Once the Chagas disease diagnosis has been confirmed, the healthcare professionals described a typical treatment plan that could include baseline and serial echocardiograms, baseline titers, chest x-rays, and bi-weekly lab works to monitor if the prescribed medication is effective.

Access to Treatments

Patients and healthcare professionals noted the challenges that patients have faced in waiting for treatments, including medications and surgical intervention. Maria and Candace shared their experiences with long wait times in obtaining medications through the CDC program for treating Chagas disease, with Candace noting she waited six months after diagnosis to begin treatment. Participating healthcare professionals provided their perspectives on the challenges that Chagas patients face in accessing treatments in the United States, including financial, language, and geographical barriers.

Perspectives on Clinical Trials

⁵For more information, see the CDC’s website on National Notifiable Diseases Surveillance System: <http://www.cdc.gov/nndss/>

To further understand patient perspectives on treatments, patient panelists were asked to consider a hypothetical scenario (see full text in Appendix 3) regarding a clinical trial on a treatment for Chagas disease. With only minimal information provided on what the trial entails, patients were asked to share what thoughts or considerations come to mind as they decide whether they would be interested in enrolling in the study. Patient panelists who participated in this exercise unanimously agreed that they would participate in the trial, regardless of the side effects mentioned. Below are excerpts of their responses:

- “I don't have to think about it. I would jump on it. I don't want someone else to end up with [cardiac complications].”
- “If I could be your guinea pig for you to learn, by all means, go ahead. If it can help us get better treatment, bring out awareness, why not?”
- “We want to help in time so they [future patients] don't get to these consequences that we have.”

Perspectives on Ideal Treatments

In addition to the need for increased awareness and education across the healthcare community, participants also identified what they considered to be aspects of an ideal treatment for Chagas. They include treatments that could be administered or received more locally to avoid the burden of travel, treatments with fewer side effects, and earlier diagnosis and treatment.

Highlights of Scientific Workshop

FDA held a scientific workshop in the afternoon of April 28 to further explore several issues related to drug development for Chagas disease, such as clinical trial design and endpoint studies. This workshop enabled patients, academic experts, healthcare providers, government officials, industry, and advocacy organizations to share their perspectives on these aspects of Chagas disease. The workshop was split into presentation and discussion segments.

The presentations began with an overview (Caryn Bern, University of California San Francisco) of the epidemiology and natural history of Chagas disease. Dr. Bern examined several areas of Chagas disease, including: the modes of transmission; the current estimated patient population in Latin America and the United States; difficulty estimating the extent and spread of Chagas in the United States, the disease symptoms and progression for infected patients; the various tests used to diagnose Chagas disease; and the effectiveness of current treatment options.

The second presentation (Joseph Toerner, FDA) examined review considerations for new drugs in the United States. Dr. Toerner first provided a general overview of adequate and well-controlled clinical trials, including the need to demonstrate safety and efficacy, the statutory standards for efficacy trials, and the five types of trials specifically outlined in FDA's regulations (placebo control, dose comparison, treatment concurrent control, active treatment control, and historical control). Dr. Toerner then explored endpoints in clinical trials, defining them according to statute and providing examples of three types of endpoints: clinician-reported outcomes, patient-reported outcomes, and biomarkers. He concluded with a brief discussion on the standard and accelerated approval pathways at FDA.

The third presentation (Isabela Ribeiro, Drugs for Neglected Diseases Initiative) addressed recent, ongoing, and planned clinical trials for Chagas disease. Dr. Ribeiro provided background on past clinical trials for the two existing treatments for Chagas disease, both developed in the 1960's and 1970's (nifurtimox and benznidazole). She then focused on the lack of clinical trials prior to the early 2000's, as well as the lack of treatment options for both pediatric and adult patients with chronic Chagas. Dr. Ribeiro highlighted the transition in recent trials from using serology as an endpoint to using polymerase chain reaction, and provided background for ongoing trials for patients with chronic Chagas. She concluded with an overview of planned and early-stage clinical trials examining benznidazole, nifurtimox, and other compounds for both children and adults.

A panel discussion followed these presentations, addressing topics of patient enrollment, clinical trials, and drug approval for Chagas disease. The discussion on patient enrollment touched on the inclusion of children in clinical trials and the viability of clinical trials for acute vs. chronic Chagas. One participant was strongly in favor of including children with chronic Chagas in clinical trials. Another participant agreed that a study of children could be feasible, but questioned whether the findings would be representative of an adult population, who tend to have more severe outcomes. Participants generally agreed that future trials should focus on patients with chronic Chagas, including one participant who called clinical trials for acute Chagas patients unfeasible given the nature of the disease.

The discussion also touched on several challenges in developing clinical trials for Chagas disease. One difficulty identified by several participants was not being able to contact patients for follow-up after clinical trials. Participants noted that patients often did not have the financial means, moved frequently, and occasionally visited endemic areas and were re-infected with Chagas disease. Another difficulty mentioned was the challenge in implementing control groups. One participant commented that it is very difficult to deny treatment to infected patients, especially when treatment has been available for decades in endemic countries.

Following the first panel discussion, the workshop resumed with two presentations followed by a final panel discussion on clinical trial design and endpoints for Chagas disease. The first presentation (Louis Kirchhoff, University of Iowa) provided detail on the use of serology as an approach for detecting parasitologic cure for Chagas disease. Dr. Kirchhoff also touched upon general challenges facing clinical trial design for Chagas disease, including a lack of timely clinical outcomes (due to the long-term nature of disease symptoms) and difficulty determining whether parasitologic cure has been achieved during a trial.

The second presentation (Alejandro Schijman, Research Institute of Genetic Engineering and Molecular Biology) focused on using polymerase chain reaction (PCR) as a surrogate marker for monitoring treatment efficacy. Dr. Schijman provided a brief overview of the history of PCR, its use by the World Health Organization, and efforts to identify the most reliable PCR test in use. He then examined studies applying PCR for treatments for Chagas disease, as well as data supporting the usefulness of PCR in the short term to show treatment failure.

The panel discussion that followed addressed clinical trial design for Chagas disease. Participants generally agreed that placebo concurrent control trials would be acceptable for adults with chronic Chagas, but not for children. Options mentioned for trials aimed at children included a dose comparison concurrent design, an active treatment concurrent design, or a historical control. The discussion also touched on dose levels and duration of treatment, exploring treatment for 30 versus 60 days. The second part of the panel discussion covered endpoints for Chagas disease. Participants noted the

difficulty in selecting and using an endpoint, and generally agreed that more information was needed to be able to select either PCR or serology as a more effective method of measuring treatment effect.

Conclusion

As described in this report, this meeting emphasized the urgent need for increased awareness and available treatments for Chagas disease. This Patient-Focused Drug Development meeting provided FDA the unique opportunity to hear directly from patients about the significant physical and emotional burden of Chagas disease. The scientific component of the meeting further allowed FDA to obtain expert input on the complex issues surrounding drug development and treatment of Chagas disease more broadly, including clinical trial design and conduct. FDA is truly grateful to the patients, patient representatives, physicians, and scientific experts who provided us with an understanding of the impact on Chagas disease on patients' daily life, the burden of treatments, and what they hope for in future treatments.

It is clear that the challenges facing Chagas patients are numerous, and are not just limited to physical symptoms. We are so thankful to the patient panelists who so thoughtfully and courageously shared their personal experiences. FDA shares the patient and healthcare community's desire to furthering the development of safe and effective drug therapies to treat or prevent Chagas disease.

Appendix 1: Meeting Agenda and Discussion Questions



Chagas Disease Public Meeting on Patient-Focused Drug Development



April 28, 2015

8:00 – 9:00 am	Registration
9:00 – 9:05 am	Welcome Soujanya Giambone, MBA <i>Office of Strategic Programs (OSP), Center for Drug Evaluation and Research (CDER), FDA</i>
9:05 – 9:10 am	Opening Remarks John Farley, MD MPH <i>Deputy Director, Office of Antimicrobial Products (OAP), CDER, FDA</i>
9:10 – 9:20 am	Overview of FDA's Patient-Focused Drug Development Initiative Theresa Mullin, PhD <i>Director, OSP, CDER, FDA</i>
9:20 – 9:35 am	An Overview of Chagas Disease and Available Treatment Maria Allende, MD <i>Medical officer, Division of Anti-infective Products (DAIP), CDER, FDA</i>
9:35 – 9:40 am	Overview of Discussion Format Soujanya Giambone, MBA <i>OSP, CDER, FDA</i>
9:40 – 10:00 am	Panel #1 Comments on Topic 1 Topic 1: Disease symptoms and daily impacts that matter most to patients. A panel of patients and patient advocates will provide comments to start the discussion.
10:00 – 10:30 am	Panel Discussion on Topic 1
10:30 – 10:40 am	Break
10:40 – 11:00 am	Panel #2 Comments on Topic 2 Topic 2: Patient perspectives on current approaches to treating Chagas disease. A panel of patients and patient advocates will provide comments to start the discussion.
11:00 – 11:45 am	Panel Discussion on Topic 2
11:45 – 12:45 pm	Lunch
Session 2: Scientific Discussion	

12:45– 1:05 pm	The Epidemiology and Natural History of Chagas Disease Caryn Bern, MD MPH <i>University of California, San Francisco</i>
1:05 – 1:20 pm	Review Considerations for New Drugs in the United States Joe Toerner, MD MPH <i>CDER/FDA</i>
1:20 – 1:50 pm	Recent, Ongoing, and Planned Clinical Trials for Chagas Disease Isabela Ribeiro, MD <i>Drugs for Neglected Diseases Initiative (DNDi), Geneva, Switzerland</i>
1:50 – 2:30 pm	Panel Discussion Moderator: Sumathi Nambiar, MD MPH <i>CDER/FDA</i>
	Populations who could be enrolled in a clinical trial and acceptable control groups
	<ul style="list-style-type: none"> • <i>What are the populations (e.g. stage of disease) for which a clinical trial could be feasible and acceptable?</i> • <i>Are there any situations for which a placebo control would be acceptable?</i>
2:30 – 2:45 pm	Break
2:45 – 3:15 pm	Laboratory Monitoring Using Serology Louis Kirchhoff, MD, MPH <i>University of Iowa Carver College of Medicine, Iowa City, Iowa</i>
	Laboratory Monitoring Using PCR Alejandro Schijman, PhD <i>Research Institute of Genetic Engineering and Molecular Biology, Buenos Aires, Argentina</i>
3:15 – 4:30 pm	Panel Discussion Moderator: Sumathi Nambiar, MD MPH <i>CDER/FDA</i>
	Trial designs and trial endpoints
	<ul style="list-style-type: none"> • <i>What are feasible and acceptable clinical trial designs?</i> • <i>What primary endpoint(s) would be appropriate for a clinical trial? What are the strengths and weaknesses of clinical outcome endpoints (For example, Is the clinical outcome endpoint well-defined and reliable? When should treatment benefit be assessed? How long would patients need to be followed?)</i> • <i>What are the strengths and weaknesses of the evidence that change in serology (sero-negative or reduction in titers), negative PCR, or other laboratory test result at a specified time point after treatment are predictive of later clinical outcome?</i>
4:30 – 4:50 pm	Open Public Comment Session
4:50 – 5:00 pm	Closing Remarks and Adjourn

Discussion Questions (Morning Session):

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

1. What **worries you most** about your condition?
2. 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 irregular heartbeat, shortness of breath, difficulty swallowing, stomach pain or constipation)
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 condition? (Examples of activities may include sleeping through the night, daily hygiene, driving, being a blood or organ donor, or for women in reproductive age concern about getting pregnant and transmitting the infection to your children, etc.)
4. How have your condition and its symptoms **changed over time**?
5. Do your symptoms come and go? If so, do you know of anything that makes your symptoms better or worse?

Topic 2: Patient Perspectives on Current Approaches to Treat Chagas Disease:

1. **What are you currently doing** to help treat your condition? (Examples may include prescription medicines, over-the-counter products, and other therapies including non-drug therapies such as diet modification.)
 - a. What specific symptoms do your treatments address?
 - b. How has your treatment regimen changed over time, and why?
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, length of treatment, number of pills to take daily, going to the hospital for frequent check-up or treatment, restrictions on driving, potential consequences to your health and your child's health during pregnancy, etc.)
3. What specific things would you look for in an **ideal treatment** for your condition?

Appendix 2: FDA and Patient Panel Participants

Patient Panel

- Carlos – Patient
- Maria – Patient
- Candace – Patient
- Maira – Patient
- Rachel – Advocate

FDA Panelists

- Maria Allende (Medical Officer, Division of Anti-Infective Products, Center for Drug Evaluation and Research (CDER))
- Jonca Bull (Director, Office of Minority Health, Office of the Commissioner)
- Edward Cox (Director, Office of Anti-Microbial Products (OAP, CDER))
- John Farley (Deputy Director, OAP, CDER)
- Jonathon Goldsmith (Acting Associate Director, Rare Disease Program, Office of New Drugs, CDER)
- Theresa Mullin (Director, Office of Strategic Programs, CDER)
- Sumathi Nambiar (Director, Division of Anti-Infective Products (DAIP), CDER)
- Thomas Smith (Medical Team Leader, DAIP, CDER)
- Joseph Toerner (Deputy Director for Safety, DAIP, CDER)
- Kathleen Whitaker (Senior Scientific Reviewer, Division of Microbiology Devices, Center for Devices and Radiological Health)

External Panelists

- Jaime Altcheh, MD (Chief, Parasitology Service, Hospital de Niños Ricardo Gutierrez, Buenos Aires, Argentina)
- Caryn Bern, MD, MPH (Professor of Epidemiology and Biostatistics, University of California, San Francisco)
- Danong Chen, PhD (Chief Executive Officer, MetronomX Therapeutics, LLC)
- Barbara Herwaldt, MD, MPH (Medical Epidemiologist, Division of Parasitic Diseases, U.S. Centers for Disease Control and Prevention)

- Louis Kirchhoff, MD, MPH (Professor of Internal Medicine and Infectious Diseases, University of Iowa Carver College of Medicine)
- Rachel Marcus, MD (Cardiologist, Washington Hospital Center, Washington, DC, LASOCHA (Latin America Society of Chagas))
- Sheba Meymandi, MD (Cardiologist, Director, Center of Excellence for the Diagnosis and Treatment of Chagas Disease, Olive View UCLA Medical Center, Sylmar, CA)
- Isabela Ribeiro, MD (Head, Chagas Clinical Program, Drugs for Neglected Diseases Initiative (DNDi) Geneva, Switzerland)
- Alejandro Schijman, PhD (Laboratory of Molecular Biology of Chagas Disease, Research Institute of Genetic Engineering and Molecular Biology Dr. Héctor N. Torres, Buenos Aires, Argentina)
- Sergio Sosa Estani, MD, MPH, PhD (Director, National Institute of Parasitology, Buenos Aires, Argentina)
- Kiliana Suzart-Woischnik, MD MPH (Senior Epidemiologist, Bayer Healthcare)

Appendix 3: Meeting Scenario Questions

Scenario 1: Would you consider this treatment: For yourself? For your teenage child?

- Imagine you are just diagnosed with Chagas disease.
 - You have no symptoms.
 - You may have had the disease for 2-3 decades.
 - 3 out of 10 patients who have no symptoms may develop symptoms that will lead to sudden death from heart conditions (usually around the age of 40)
- Drug X is developed to treat patients with Chagas disease
 - Patients will need to take Drug X for 60 days.
 - Drug X has been shown to cure 7 out of 10 patients that do not have symptoms of Chagas disease
 - Drug X causes nausea, vomiting or tingling or numbness in arms or legs in many patients. In rare cases, it causes non-fatal, reversible side effects such as seizures.

Scenario 2: What thoughts and questions come to mind as you hear this scenario?

- You have been invited to participate in a clinical trial to study an experimental treatment for Chagas disease
- Early research in animals and people shows that this treatment may cure the disease in some people
- The purpose of the study is to better understand how well this treatment works and its safety
- The study will enroll 50 adults who have been diagnosed with Chagas disease but do not show symptoms
- This clinical study lasts 2 years and clinic visits will occur every 2 months for the first year, and once every 4 months in the second year
- Some visits may involve blood tests
- More common side effects of this therapy may include nausea, vomiting, and weight loss.
- Rarer but more serious side effects may include changes in sensation and nerve damage and skin rash

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

Introduction

Over the past several years, FDA has developed an enhanced structured approach to benefit-risk assessment in regulatory decision-making for human drugs and biologics⁶. 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 Chagas 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 Chagas disease below draws from various sources, including what was discussed at the Chagas disease Patient-Focused Drug Development meeting held on April 28, 2015. This sample framework contains the kind of information that we anticipate could be included in a framework completed for a drug under review for Chagas disease. This information is likely to be added to or changed over time based on a further understanding of the condition or changes in the treatment armamentarium.

⁶ 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>.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<ul style="list-style-type: none"> – Chagas is a disease spread by contact with feces of an infected insect (triatomine) carrying a parasite called <i>Trypanosoma cruzi</i>. – The disease is estimated to affect around 6-7 million people worldwide, primarily in rural areas in Latin America. In the United States, the disease is estimated to affect more than 300,000 people, most of whom acquired the disease in foreign countries. – There are two phases of Chagas disease: the acute phase and the chronic phase. The acute phase is often asymptomatic and can last a few weeks/months after infection. The chronic phase may last decades after infection, and patients may develop more significant symptoms, including problems with swallowing, digestion, constipation or abdominal pain, and heart failure. – Chagas disease can have significant physical and emotional impact on patients' quality of life. 	<p>Chagas disease is a serious disease with potentially life-threatening complications (such as heart failure) that can have a significant impact on patients' quality of life.</p>
Current Treatment Options	<ul style="list-style-type: none"> – There are currently no drugs approved by FDA to treat Chagas disease. – Two treatments are available exclusively from the Centers for Disease Control and Prevention at the request of a physician: benznidazole and nifurtimox. <ul style="list-style-type: none"> ○ Benznidazole and nifurtimox are primarily intended for patients with acute Chagas and children under 18 with chronic Chagas. They may also be helpful for adult patients with chronic Chagas. – Side effects for both drugs are fairly common, and tend to increase in frequency and severity as patients age. <ul style="list-style-type: none"> ○ Side effects of benznidazole include allergic dermatitis, peripheral neuropathy, anorexia and weight loss, and insomnia ○ Side effects of nifurtimox include anorexia and weight loss, polyneuropathy, nausea, vomiting, headache, and dizziness or vertigo – Other treatments for Chagas disease focus on managing the symptoms of the disease, specifically gastrointestinal problems and heart failure. Treatments for Chagas patients with cardiac issues may include invasive surgical procedures, use of implantable medical devices, and heart transplants. 	<p>There is an unmet need for FDA-approved therapies for all patients with Chagas disease, including adult patients with chronic Chagas disease.</p>