

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

Functional Gastrointestinal Disorders

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Center for Drug Evaluation and Research (CDER)
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Introduction

On May 11, 2015, FDA held a public meeting to hear perspectives from patients living with functional gastrointestinal (GI) disorders, their caregivers, and other patient representatives on the most significant effects of these disorders and currently available therapies. FDA conducted the meeting as part of the agency's Patient-Focused Drug Development initiative, an FDA commitment under the fifth authorization of the Prescription Drug User Fee Act (PDUFA V) to more systematically gather patients' perspectives on their condition and available therapies to treat their condition. As part of this commitment, FDA is holding at least 20 public meetings between Fiscal Years 2013 - 2017, each focused on a specific disease area. More information on this initiative can be found at <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm326192.htm>.

Overview of functional gastrointestinal disorders

Functional gastrointestinal (GI) disorders describes a group of common, chronic GI conditions that affect a part of the GI tract and are often characterized by chronic time course and unpredictable symptom exacerbations. Generally, there are no anatomical, structural, or biochemical abnormalities. Diagnosis of these disorders is based on signs and symptoms using Rome Criteria. There are 28 adult and 17 pediatric functional GI disorders based on the Rome III diagnostic criteria.¹ These disorders include irritable bowel syndrome, chronic idiopathic constipation, functional dyspepsia, gastroparesis, and functional abdominal pain. Functional GI disorders are highly prevalent and impact across all demographics; approximately two out of every five people are affected by a functional GI disorder. There is much overlap between these disorders, and many patients suffer from two or more functional GI disorders.

The effects of functional GI disorders vary depending on the underlying disorder; however, common signs and symptoms of functional GI disorders relate to abnormal intestinal motility, abnormal intestinal perception, and/or abnormal brain-gut communication. Common symptoms include abdominal pain, heartburn, abdominal distention, nausea, vomiting, bloating, constipation, and/or diarrhea.

Current therapies are limited for functional GI disorders. Prescription therapies such as lubiprostone, linaclotide, metoclopramide, and alosetron are available to manage some of the symptoms. Over-the-counter treatments, including antidiarrheals, pro-motility agents, proton pump inhibitors, and H2 blockers, are also often incorporated into treatment regimens. Other therapies include dietary management, off-label, and investigational therapies. In severe cases, gastric electrical stimulation, feeding tubes, or surgical intervention may be required.

Meeting overview

This meeting gave FDA the opportunity to hear directly from patients, caretakers, and other patient representatives about their experiences with functional GI disorders and their treatments. Discussion focused on two key topics: (1) the effects of functional GI disorders that matter most to patients and (2) patients' perspectives on treatments for functional GI disorders. The discussion questions (*Appendix 1*) were published in a [Federal Register notice](#) that announced the meeting.

¹ The Rome criteria is a system developed to classify functional gastrointestinal (GI) disorders, disorders of the digestive system in which symptoms cannot be explained by the presence of structural or tissue abnormality, based on clinical symptoms. For more information: <http://www.romecriteria.org/>

For each topic, a panel of patients and patient representatives (*Appendix 2*) shared comments to begin the dialogue. Panel comments were followed by a facilitated discussion inviting comments from other patients and patient representatives in the audience. An FDA facilitator led the discussion, and a panel of FDA staff (*Appendix 2*) asked follow-up questions. Participants who joined the meeting via live webcast (referred to in this report as web participants) were also able to contribute 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 as well as how many participants shared a particular perspective on a given topic.

Approximately 25 functional GI disorder patients or patient representatives attended the meeting in-person, and approximately 40 patients or patient representatives provided input through the live webcast. According to their responses to the polling questions, the majority of meeting participants were women, ranging from 18 years to 60 years old. In-person and web participants represented a number of functional GI disorders, including (but not limited to): irritable bowel syndrome, gastroparesis, chronic persistent symptomatic gastroesophageal reflux, and chronic idiopathic constipation. Although participants at this meeting may not fully represent the population living with functional GI disorders, FDA believes that the input received during the meeting reflects a range of experiences of those conditions described above.

To supplement the input gathered at the meeting, patients and others were encouraged to submit comments on the topic to a public docket,² which was open until July 13, 2015. Forty comments were submitted to the public docket by patients and other stakeholders. The comments received via the public docket have been incorporated into this summary.

More information, including the archived webcast and meeting transcript, is available on the meeting website: <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm430885.htm>.

Report overview and key themes

This report summarizes the input provided by patients and patient representatives at the meeting or through the webcast. It also includes a summary of comments submitted to the public docket. To the extent possible, the terms used in this summary to describe specific signs, symptoms, impacts, and treatment experiences of functional GI disorders reflect the words used by in-person attendees, web participants, or docket commenters. The report is not meant to be representative in any way of the views and experiences of any specific group of individuals or entities. There may be signs, symptoms, impacts, treatments, or other aspects of the disease that are not included in the report.

The input from the meeting and docket comments emphasized the challenge of living with a functional GI disorder, its impact on daily life, and the difficulties involved in diagnosing and treating the disorder. Several key themes emerged from this meeting:

- Functional GI disorders are a group of chronic diseases that place a significant burden on daily life and have a severe impact on how patients feel and function. Most meeting participants were diagnosed with a primary underlying functional GI disorder, in addition to a range of other

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.

GI-related disorders. Participants frequently discussed the overlap of conditions and the cyclic and recurrent tendency of symptoms. Most participants focused their comments on abdominal pain and discomfort, vomiting and nausea, fatigue, and gas and flatulence as the most burdensome signs and symptoms of their disease.

- Daily life for many patients living with a functional GI disorder revolves around managing their condition and their treatments. Participants described their inability to eat, difficulty with basic tasks requiring exertion, difficulty interacting with friends and family, limitations on their ability to work, and the emotional impact on patients and caregivers.
- Although the specific treatments vary widely across the spectrum of functional GI disorders, participants shared common experiences while using a combination of drug and non-drug treatments. Participants commented on their experiences with pharmaceutical treatments addressing specific symptoms (such as nausea), strict dietary control, and non-drug therapies. Participants largely focused on the downsides of these treatments and the significant burden of a trial and error therapy regimen.

The patient input generated through this Patient-Focused Drug Development meeting and public docket comments strengthens FDA's understanding of the burden of functional GI disorders on patients and the treatments currently used to treat functional GI disorders and their symptoms. FDA staff will carefully consider this input as it fulfills its role in the drug development process, including when advising sponsors on their drug development programs and when assessing products under review for marketing approval. For example, *Appendix 4* shows how this input may directly support our benefit-risk assessments for products under review. This input may also be of value to the drug development process more broadly. For example, the report may be useful to drug developers as they explore potential areas of unmet need for patients with a functional GI disorder. It could also point to the potential need for a better understanding of particular effects of disease, such as the manifestation of fatigue or for the development and qualification of a more appropriate pain scale in clinical trials.

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

The first discussion topic focused on patients' experiences with symptoms of their functional GI disorder(s) and the impact these symptoms have on their daily lives. FDA was particularly interested in hearing patients describe how their condition and symptoms have changed over time, as well as specific activities patients could no longer do at all, or as fully as they would like to, due to their condition.

Four panelists provided comments to start the open dialogue. They included:

- Panelist 1: a woman diagnosed with gastroparesis, esophageal dysmotility, small intestinal dysmotility, and colonic inertia (which led to the removal of her colon)
- Panelist 2: a woman diagnosed with irritable bowel syndrome (IBS) a year and a half ago, although she experienced symptoms for many years before her diagnosis
- Panelist 3: a 35-year old woman diagnosed with severe gastroparesis

- Panelist 4: a woman diagnosed with a mitochondrial disorder, autonomic dysfunction, gastroparesis, overall gut dysmotility of her entire GI tract, esophageal spasms, intestinal spasms, biliary dyskinesia with a smooth muscle disorder, pancreatitis, chronic constipation, and hypoglycemia myoclonus.

The panelists detailed the difficulty of living with their respective conditions and the physical, emotional, and social impacts of their disease symptoms on their daily lives and on the lives of their loved ones. Their comments highlighted the wide variability in functional GI disorders and their manifestations. Patients and patient representatives in the audience indicated by a show of hands that the panelist comments resonated with their own experiences. The large-group discussion that followed the panel comments provided further insight into how symptoms manifest and how they change over time. The range of symptoms discussed in-person and web participants are described in more detail below.

Perspectives on most significant symptoms

Discomfort and abdominal pain

In a polling question (*Appendix 3, Q7*), participants were asked to identify up to three upper-GI related symptoms that have the most significant impact on daily life. Abdominal pain or discomfort was identified by over three-fourths of in-person and web participants as being one of their most significant symptoms. Throughout the discussion, many participants echoed that these symptoms are among the most impactful on the daily life and well-being of patients with a functional GI disorder.

Participants distinguished abdominal discomfort and abdominal pain as separate symptoms. They described abdominal discomfort as a pervasive issue that lasts “hours and hours” or is present on a “daily basis,” while abdominal pain was described as often temporary and triggered by specific foods and drinks. Discomfort was described as a “duller pain,” and a participant elaborated, “I can do things to... ignore [the discomfort], but it’s still there.” Abdominal pain was described as “crippling,” and one participant shared that during a “flare-up...it gets so bad it hurts to breathe, because [the stomach] pushed up on your lungs and it hurts.”

Participants also commented on the need for an appropriate pain scale that helps patients and their medical providers differentiate between discomfort and pain. One participant shared, “our pain is not on that scale.” Other participants added that there needs to be an increased awareness in the medical community that there are varying types of abdominal pain (e.g., constipation pain, intestinal spasms), and such distinctions would in turn help with proper diagnosis and treatment.

Participants identified eating and drinking as frequent triggers of “flare ups” or abdominal pain. A participant commented, “vegetables, even if they’re juiced, will turn my stomach and make it into such pain that I’m on the floor... or in my bed in a ball.” Other participants shared similar experiences; some commented that their pain was triggered by dairy, high fiber or fatty food consumptions.

Nausea and Vomiting

In a polling question (*Appendix 3, Q7*), two-thirds of in-person and web participants identified nausea and vomiting as significant signs and symptoms that impacted their daily life. Many participants described living with chronic nausea, which as one participant explained is like “being seasick all the

time.” Some participants described persistent and debilitating vomiting; in one example, one participant described vomiting 20 to 30 times per day in the early stage of her disease. A few participants acknowledged that as their disease progressed, they “managed to get a handle” or decrease the number of times they vomited daily, but that the nausea remained constant. Participants also shared the resulting impacts of persistent nausea and vomiting; these included pain, inability to eat a full meal, and inability to concentrate.

Fatigue

Many participants identified fatigue as one of the most significant symptoms of functional GI disorders impacting their daily life. As one participant summarized, “I have fatigue a large part of the day...any amount of physical activity will fatigue me.” Other participants shared that their fatigue resulted in difficulty focusing and eating.

Participants commented on the lack of energy that affects their daily life. One participant shared, “On my best days, it takes an hour to get washed up and that includes the rest time.” Another participant commented, “I was so tired, I’d start to fall asleep at work and go straight to bed when I got home.” One web participant commented that her fatigue worsened as the day progressed, and shared that by the end of the day “I end up dragging myself on the floor.” Several participants also discussed muscle fatigue, with one participant saying “my muscles hurt so bad, it hurts to walk.”

Abdominal distention or bloating

Nearly half of the participants indicated abdominal distention or bloating as a significant symptom. A panelist diagnosed with IBS shared that bloating is a daily occurrence for her, and often leads to other symptoms including pain and unpredictable bowel movements. She explained further, “I have bloating so bad, I can’t even fit into my work clothes. I just have a range of clothes that I...pick on a daily basis.” A webcast participant added that her bloating is “so intense that it makes it difficult to breathe.”

Lower-GI related symptoms

In a polling question (*Appendix 3, Q8*), participants were asked to identify the lower-GI related symptoms that have the most significant impact on daily life. Nearly all of the meeting participants indicated gas or flatulence as a significant symptom of their condition, followed by diarrhea and incontinence. They also commented that these symptoms had broad impacts. As one participant noted, “gas is extraordinarily painful if it’s stuck”; this comment resonated with other participants who also correlated gas and flatulence to other GI-related symptoms, such as constipation, diarrhea, and incontinence.

Three-fourths of the participants indicated in the same polling question that constipation was a major symptom of their condition. One participant shared that “it [stool] feels like I’m passing razor blades.” Many participants also observed that constipation is often a side effect of their prescription medicines. This was especially emphasized by webcast participants diagnosed with gastroparesis.

Overall impact of a functional GI disorder on daily life

Participants also described the physical, social, and emotional impact that their functional GI disorder has had on their lives, including:

- **Inability to eat.** Participants highlighted their difficulty eating or inability to eat as a major impact of living with a functional GI disorder. Most participants shared that the inability to eat had significant physical, social, and emotional impacts. One web participant commented, “The smell of food makes me really sick.” Another participant noted, “You can’t eat because you’re in pain [and] you’re nauseous.” A web participant commented on how their disease and inability to eat makes other people uncomfortable. As one participant summarized, “your life will do nothing but revolve around food and what you can’t have”; this comment resonated with many in the audience. Participants also commented on the feeling of fullness after eating only a small amount.
- **Caring for self or family.** Some participants shared their perspectives on having to rely on caregivers for daily activities, including getting dressed or exercise due to the lack of strength. One participant noted that she is unable to take normal showers because of the “weakness and blackout spells that the water instigates.” Another participant shared that she is “very limited on what I can and can’t do,” and that her husband had to alter his work schedule to help care for their children.
- **Job and school performance.** Participants shared that pain, nausea, bloating, and fatigue have made it difficult or impossible to be effective in the workplace or classroom. For example, a participant described the impact of nausea on her classwork as so debilitating that it felt like being “sick all the time.” Another participant commented that she did not want to leave the house because of her symptoms, which led to her lagging behind on work. Participants also commented on the difficulty of concentrating at work, or attending meetings where they could not “afford to have an episode.”
- **Emotional and social impacts.** Participants emphasized the many emotional and social impacts of living with functional GI disorders, including daily frustration and emotional distress. The majority of participants shared their difficulties in socializing and maintaining the sense of a “normal life” for themselves and their families. Several web participants commented that gas and flatulence were embarrassing and made it difficult to go out in social situations. Another participant explained how her condition impacted the social relationships of her children by sharing, “my kids don’t get invited to that birthday party or that meeting at school because they know I can’t make it or I’m not going to be able to eat the food.” Another participant said she lost most of her friends because she cannot “go out with friends and be able to keep up.” Other participants shared comments that their family and friends did not often understand the physical and emotional impacts of living with a functional GI disorder.

Topic 2: Patient Perspectives on Treatments for Functional GI Disorders

The second main topic of discussion focused on patients' experiences with therapies used to treat their or their loved ones' condition. Four in-person panelists and one panelist via telephone provided their comments to start the conversation. They included:

- Panelist 1: a 56-year old woman born with Hirschsprung's disease and diagnosed with gastroparesis and dysmotility of her entire digestive tract
- Panelist 2: a 45-year old woman diagnosed with gastroparesis
- Panelist 3: a woman diagnosed chronic unexplained nausea and vomiting
- Panelist 4: a 55-year old woman diagnosed with GERD, chronic constipation, and idiopathic gastroparesis
- Panelist 5: a woman diagnosed 26 years ago with diarrhea-predominant IBS

Panelists shared their experiences with a variety of treatment regimens, including prescription medications, non-drug therapies, dietary management, and other lifestyle changes. They described a process of trial and error to find an effective approach to fit their specific needs. In the large-group facilitated discussion that followed, nearly all patients in the audience indicated by a show of hands that their experiences were reflected in the panelists' comments.

Throughout the dialogue, participants detailed the benefits and downsides they have experienced from various therapies and modifications (including lifestyle changes and diet management) used to manage their condition. This section ends with participants' perspectives on ideal treatments and broader consideration regarding treatments for functional GI disorders, including the need for better understanding of the disorders for proper diagnosis (e.g., through gastric emptying studies) and treatment.

Perspectives on medical treatments for functional GI disorders

According to a polling question (*Appendix 3, Q10*), most participants reported taking or having taken drug therapies to help reduce their functional GI disorder symptoms. Prescription drug therapies were described as having widely varying degrees of effectiveness, and many participants noted they often switched therapies because they were unable to tolerate treatment side effects. Most participants also indicated that they rely on multiple therapies to help manage or treat their functional GI disorder. Their comments on experiences with specific drugs are summarized below.

The most commonly discussed treatment was Reglan (metoclopramide). One participant with gastroparesis noted that after being put on Reglan, she was able to start eating regularly and "suffered less nausea and dizziness"; however, she continued to suffer from severe fatigue. Another participant commented that Reglan was a promising treatment for her when she first started the treatment, but she "quickly started developing some early tardive dyskinesia-type symptoms." Other participants shared significant downsides to Reglan including more frequent vomiting, restless leg syndrome, and neurological side effects. A few participants also shared experiences where Reglan did not improve their symptoms at all.

Several participants commented that domperidone³ was a part of their treatment regimen. One participant with gastroparesis commented that upon taking domperidone, she had “immediate, complete, reliable relief,” with no adverse effects. Some participants noted that higher dosages of domperidone resulted in higher hormone levels (such as prolactin); these participants shared that their physicians would make dosage adjustments accordingly. Finally, other participants commented that they were unable, unwilling, or afraid to take domperidone, since it is not an FDA-approved drug.

Participants also shared their experiences with other therapies they were using to manage their GI symptoms. Several participants shared mixed experiences with Linzess (linaclotide). One participant commented on her daily reliance on Linzess for relief, while a web participant expressed that it did not work and caused “intense pain.” Similarly, participants shared their experiences with Amitiza (lubiprostone) and included increased nausea and pain as resulting side effects. Participants also commented on their experiences with Imodium (loperamide). One participant shared that she would go back on Imodium in between alternative treatments, and that it is the “most reliable for short-term relief.”

Participants mentioned a range of other drug therapies to address their GI symptoms. These included: pain medications, a range of anti-nausea drugs (e.g., Zofran (ondansetron), promethazine), antibiotics (e.g., erythromycin, rifaximin), antipsychotics (e.g., Zyprexa (olanzapine)), antidepressants (e.g., desipramine) and Botox (onabotulinumtoxinA) injections. Several participants also described taking acid reflux medications (such as Prilosec) to treat their acid reflux.

Non-drug therapies

Gastric Electrical Stimulation

Several participants shared mixed experiences with gastric electrical stimulation. One participant commented that it was a “lifesaver;” however, she also commented on “getting shocks” as a downside of the device. Another participant noted that while the device signals the stomach to help reduce nausea and vomiting, it would be more useful if it, “actually assists the stomach in contracting.” One participant described the constant need to visit an emergency room to have the battery replaced, but that the device is “worth investigating” for those “who are having a terrible time, because any relief can be better than nothing.”

Dietary management

Various dietary controls were identified as an essential component of treatment by many participants. One participant shared that her diet cannot include any fats or oils, while another web participant commented on eliminating genetically modified foods from the diet. Participants noted that the strict dietary restrictions placed a significant burden on their daily lives. A wide variety of vitamins, herbs and dietary supplements were mentioned as being used to treat specific symptoms, including Vitamin D, fish oil, mint, glutamine, deactivated charcoal, probiotics and digestive enzymes.

³ Domperidone is not currently approved for marketing in the U.S. Patients 12 years of age and older with certain gastrointestinal (GI) conditions may be able to receive treatment with domperidone through an expanded access investigational new drug application (IND). For more information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm368736.htm>.

Other non-drug therapies

Several participants mentioned that medical marijuana was effective in treating their pain and nausea. Other non-drug or physical therapies were also mentioned including acupuncture, massage, heating pads, homeopathic remedies, and visiting a chiropractor. Overall, participants noted some level of relief from these treatments.

Treatment downsides

Below is a summary of the challenging aspects of various treatments participants shared during this meeting.

- Many participants described the significant impact of treatment side effects. One participant stated, “I have not found a medication which I could take which does not make me tired or make my head foggy.” One participant, whose treatment regime includes a patient-controlled analgesia (PCA) pump for her total parenteral nutrition (TPN), commented, “I’ve had multiple episodes of sepsis...I’ve lost a lot of functional ability.”
- Some participants commented that side effects of a treatment can worsen symptoms of the underlying disease or introduce new bothersome GI effects. For example, a web participant commented that trying to manage her pain with pain medications resulted in slowed digestion, which was “equally debilitating.”
- Some participants shared that weight gain is the most visible of their treatment side effects, but expressed concerns on the long-term effects of their treatments and how the side effects worsened with prolonged use. Participants also commented on the balance between being underweight due to the symptoms and then experiencing unwanted weight gain due to the side effects of their treatments.
- Some participants commented that their therapies worked well initially, but became less effective with time. One participant commented on how she went back on Imodium (loperamide), but “it didn’t work completely and I was getting a rebound effect.” The same participant also noted that she developed a tolerance for Imodium, and as a result kept having to take “more and more.”
- Participants commented on the burden of their treatment regimes, including one participant who stated, “Every day I take over ten different medications to treat my symptoms, including four medications specifically for nausea.” Another participant commented that in the process of trying different medications, “you just feel like a lab rat.”
- Participants commented on the burden of treatment, including out-of-pocket costs for treatments not covered by insurance.

Perspectives on an ideal treatment for functional GI disorders

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

- Participants commented on the need for increased awareness and medical knowledge of functional GI disorders by medical professionals. Participants stressed that proper diagnosis is critical to successful management and treatment of their condition. Many participants described their own difficulty in receiving a diagnosis (including being misdiagnosed), highlighting the lack of appropriate diagnostic tools. For example, one participant currently diagnosed with chronic unexplained nausea and vomiting shared that she had previously been diagnosed with gastroparesis because “sometimes I pass and sometimes I fail the gastric emptying studies.”
- Short of a cure, many participants expressed the need for effective treatments that can better address the underlying cause of their disease, with less burdensome side effects. One participant reiterated that patients with a functional GI disorder often are unable to tolerate the side effects of their treatments and expressed that an ideal treatment would be a “gentle medication or supplement... that would not lead to tolerance.”
- Several participants noted the need for fast-acting therapies that could control nausea, gas, or incontinence, and in turn provide them with the confidence that they would not have “accidents” in public. One participant shared that a fast-acting therapy would help to “gain some security wherever I am.”
- Participants stressed the need for a treatment regimen that would enable them to have a more nutritious diet and also reduce their susceptibility to other diseases due to lack of nutrition. One web participant commented, “I need to be able to eat more than 500 calories daily so I can improve my quality and participation in life.”

Summary of Comments Submitted to the Public Docket

FDA received approximately 40 comment submissions to the public docket that supplemented the Patient-Focused Drug Development meeting on functional GI disorders. The majority of these comments were submitted by participants living with a functional GI disorder or their caregivers. FDA also received comments from advocacy organizations, including Gastroparesis Patient Association for Cures and Treatments, Critical Path Institute’s Patient-Reported Outcome Consortium’s Irritable Bowel Syndrome Working Group, International Foundation for Functional GI Disorders, Professional Compounding Centers for America, and the Celiac Disease Foundation.

The docket comments echoed the experiences and perspectives shared by participants of the meeting on the symptoms that affected their lives the most, the impacts of their disease on daily life, and their experiences with treatments for functional GI disorders. In the summaries that follow, particular focus is placed on experiences or perspectives that were not raised or addressed in detail at the public meeting.

Submitted comments on symptoms of functional GI disorders

The symptoms of functional GI disorders mentioned on the docket reflected those discussed during the meeting. The most commonly mentioned symptoms included nausea, vomiting, abdominal pain, bloating, and fatigue. Other symptoms mentioned included acid reflux, colon spasms, cramping, insomnia, heartburn, and chronic dehydration. One commenter shared that her functional GI disorder resulted in pre-cancerous polyps in her stomach and intestines.

Several commenters expanded on the triggers for their GI-related symptoms. One participant shared that eating throughout the day significantly worsened her symptoms. She elaborated, “I must choose between eating and pain every single day.” Other commenters noted that stress and hormone fluctuations significantly exacerbated their GI-related symptoms.

Submitted comments on the overall impact of functional GI disorders on daily life

The docket comments reflected the input received during the meeting related to the impact of functional GI disorders on patients’ daily lives, and its significant toll on patients and their families. Most commenters shared that participating in physical activity has become very limited due to their conditions. As one commenter reiterated, “There are a limited number of things I can do with a group since I tend to have a reaction so easily.” Commenters also echoed the impact of living with a functional GI disorder on family life, school and job performance and their inability to eat. One participant described her disorder as an “invisible illness” where “nothing makes you feel back to 100%.”

Submitted comments on current treatments for functional GI disorders

The submitted comments reiterated the challenges of managing the many symptoms of functional GI disorders. The range of commenters’ experiences was similar to the experiences shared at the public meeting. The prescription drug therapies mentioned most frequently were Reglan and domperidone. Non-drug therapies, such as dietary modifications, were also frequently mentioned. Commenters’ experiences with prescription and non-drug therapies emphasized the variability of benefits and side effects from different patients. More detail is provided below.

- **Drug therapies:** One commenter shared that they had severe side effects while on Reglan, including high blood pressure and tachycardia. One commenter whose treatment regime includes domperidone stated that without her medications she is “completely bedridden,” however, she commented that her medications don’t improve her condition “to do much of anything except get out of bed.” Another commenter reported that Linzess (linaclotide) does allow bowel movements, but is associated with “bloating and cramping/pain/discomfort ... [and] diarrhea for 2 to 3 hours after taking Linzess.” A range of other drug therapies were mentioned, including Wellbutrin (bupropion), pain medications, anti-spasm medications, anti-psychotic medications and over-the-counter laxatives (such as MiraLax).
- **Medical devices or surgical treatments:** Medical devices or surgical treatments (such as a feeding tube) and IV therapy (such as TPN) were also mentioned. However, commenters also shared the downsides to medical procedures; one commenter shared that with TPN therapy, there was always a “fear of central line sepsis and liver failure.” One commenter living with IBS shared that they had fecal microbiome transplants.
- **Non-drug therapies:** Discussion on non-drug therapies closely resembled input received during the meeting. In addition to various dietary controls, commenters also mentioned L-Glutamine, magnesium, probiotics, a gluten-free diet, essential oils, Capsicol, Seacure, Vitamin C, Vitamin B and Calcium.

Submitted comments on ideal treatments for functional GI disorders

Several perspectives were provided on ideal treatment for functional GI disorders, which reiterated the perspectives heard during the public meeting. Commenters identified the need for medications that

addressed specific symptoms, including reducing nausea and increasing the ability to eat. Some stressed the need for “palatable, high-nutritive, high-protein, concentrates, wholesome, inexpensive liquid and non-solid foods,” that were easy to digest for people living with functional GI disorders.

Conclusion

Functional GI disorders encompass a spectrum of diseases with highly variable symptoms that significantly affect a patient’s day-to-day functioning and way of life. Misunderstanding of functional GI disorders, even in the medical community, often leads to misdiagnosis, misguided treatment, and worse outcomes. This Patient-Focused Drug Development meeting provided FDA with the opportunity to hear from patients first-hand of the emotional, social, and physical toll that their condition has on their lives and the lives of their loved ones. Considering the distinct manifestation of functional GI disorders and the often overlap of multiple conditions in each patient, FDA is grateful to have heard the patients’ voice on what symptoms, impacts, and aspects of treatments matter most to them, in addition to what factors are considered in making treatment decisions.

FDA recognizes that patients have a unique ability to contribute to our understanding of the broader context of this disease, which is important to our role, and that of others, in the drug development process. We are thankful to all of the participants who so thoughtfully and courageously shared such personal stories and perspectives. FDA shares the patient community’s desire and commitment to furthering the development of safe and effective drug therapies.

Appendix 1: Meeting Agenda and Discussion Questions



Functional Gastrointestinal Disorders Public Meeting on Patient-Focused Drug Development May 11, 2015



12:00 – 1:00 pm	Registration
1:00 – 1:05 pm	Welcome Sara Eggers, PhD <i>Office of Strategic Programs (OSP), Center for Drug Evaluation and Research (CDER), FDA</i>
1:05 – 1:10 pm	Opening Remarks Donna Griebel, MD <i>Director, Division of Gastroenterology and Inborn Error Products (DGIEP), CDER, FDA</i>
1:10 – 1:20 pm	Overview of FDA’s Patient-Focused Drug Development Initiative Theresa Mullin, PhD <i>Director, OSP, CDER, FDA</i>
1:20 – 1:30 pm	Background on Disease Area and Treatment Laurie Muldowney, MD <i>Medical Officer, DGIEP, CDER, FDA</i>
1:30 – 1:40 pm	Overview of Discussion Format Sara Eggers, PhD <i>OSP, CDER, FDA</i>
1:40 – 2:10 pm	Panel #1 Comments on Topic 1 Topic 1: Disease symptoms and daily impacts that matter most to patients. A panel of patients and patient representatives will provide comments to start the discussion.
2:10 – 2:45 pm	Large-Group Facilitated Discussion on Topic 1 Patients and patient representatives in the audience are invited to add to the dialogue.
2:45 – 2:55 pm	Break
2:55 – 3:25 pm	Panel #2 Comments on Topic 2 Topic 2: Patient perspectives on current approaches to treating functional GI disorders. A panel of patients and patient representatives will provide comments to start the discussion.

3:25 – 4:25 pm	Large-Group Facilitated Discussion on Topic 2 Patients and patient representatives in the audience are invited to add to the dialogue.
4:25 – 4:55 pm	Open Public Comment
4:55 – 5:00 pm	Closing Remarks Andrew Mulberg, MD, FAAP <i>Deputy Director, DGIEP, CDER, FDA</i>

Discussion Questions

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

- 1) Have you received a diagnosis of a functional GI disorder from a healthcare provider? If so, please state the 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 pain, bloating, constipation, vomiting)
- 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)
 - a) How do your symptoms and their negative impacts affect your daily life on the **best days**? On the **worst days**?
- 4) How has your condition and its symptoms **changed over time**?
 - a) Do your symptoms come and go or are they ongoing? If so, do you know of anything that worsens your symptoms?
- 5) What **worries you most** about your condition?

Topic 2: Patients' perspectives on current approaches to treating functional GI disorders

- 1) **What are you currently doing** to help treat your condition or its symptoms? (Examples may include prescription medicines, over-the-counter products, and other therapies including nondrug 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) **How well** does your current treatment regimen treat the most significant symptoms of your disease?
 - a) How well do these treatments stop or slow the progression of your condition?
 - b) How well do these therapies improve your ability to do specific activities that are important to you in your daily life?
 - c) How well have these treatments worked for you as your condition has 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, going to the hospital for treatment, restrictions on driving, etc.)
- 4) Assuming there is no complete cure for your condition, what specific things would you look for in an **ideal treatment** for your condition?

Appendix 2: FDA and Patient Panel Participants

Patient Panel, Topic 1

- Bettermarie Bond - Patient
- Tanya Taylor - Patient
- Carrie Reilly - Patient
- Cynthia Bens - Patient

Patient Panel, Topic 2

- Carol Pasinkoff - Patient
- Lynn Wolfson - Patient
- Meredith Holt - Patient
- Jillian Chilson - Patient
- Anne Sirota (via Phone) - Patient

FDA Panel

- Donna Griebel, Division of Gastroenterology and Inborn Errors Products (DGIEP), Office of New Drugs (OND), Center for Drug Evaluation and Research (CDER)
- Andrew Mulberg, DGIEP, OND, CDER
- Preeti Venkataraman, DGIEP, OND, CDER
- Lara Dimick, DGIEP, OND, CDER
- Laurie Muldowney, DGIEP, OND, CDER
- Sarrit Kovacs, Clinical Outcomes Assessment Staff, OND, CDER
- Theresa Mullin, Office of Strategic Programs (OSP), CDER

Appendix 3: Meeting Polling

The following questions were posed to in-person and web meeting participants at various points throughout the May 11, 2015, Functional GI Disorders Patient-Focused Drug Development meeting. Participation in the polling questions was voluntary. The results were used as a discussion aid only and should not be considered scientific data.

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. Are you/Is your loved one:
 - a. Male
 - b. Female
3. Have you/your loved one been diagnosed as having a functional GI disorder?
 - a. Yes
 - b. No
4. Which of the following functional GI disorders do you have? Choose all that apply.
 - a. Irritable bowel syndrome
 - b. Gastroparesis
 - c. Chronic persistent symptomatic gastroesophageal reflux despite standard therapeutic interventions
 - d. Chronic idiopathic constipation
 - e. Other or not sure
5. What is your/your loved one's age?
 - a. Younger than 18
 - b. 18 – 30
 - c. 31 – 40
 - d. 41 – 50
 - e. 51 – 60
 - f. 61 – 70
 - g. 71 or greater

Question for Topic 1

6. Which of the following upper- GI related symptoms have you/your loved one experienced in the past year? Choose all that apply.
- a. Vomiting or nausea
 - b. Heartburn
 - c. Feeling of fullness
 - d. Lack of appetite
 - e. Inability to eat full meal
 - f. Weight loss or malnutritional effect
 - g. Abdominal pain or discomfort
 - h. Bloating
 - i. Other upper GI symptoms, not mentioned
7. Of these upper- GI related symptoms that you experience, which have the most significant impact on your life? Choose up to three symptoms.
- a. Vomiting or nausea
 - b. Heartburn
 - c. Feeling of fullness
 - d. Lack of appetite
 - e. Inability to eat full meal
 - f. Weight loss or malnutritional effect
 - g. Abdominal pain or discomfort
 - h. Bloating
 - i. Other upper GI symptoms, not mentioned
8. Which of the following lower GI related symptoms have you/your loved one experienced in the past year? Choose all that apply
- a. Diarrhea
 - b. Constipation
 - c. Abdominal pain or discomfort
 - d. Gas or Flatulence
 - e. Incontinence
 - f. Sense of urgency
 - g. Other lower GI symptoms, not mentioned
9. Of these lower- GI related symptoms that you experience, which have the most significant impact on your life? Choose up to three symptoms.
- h. Diarrhea
 - i. Constipation
 - j. Abdominal pain or discomfort
 - k. Gas or Flatulence
 - l. Incontinence
 - m. Sense of urgency

- n. Other lower GI symptoms, not mentioned

Questions for Topic 2

10. Have you ever used any of the following prescription or investigational drug therapies to help reduce the symptoms of functional GI disorders? Check all that apply.

- a. Amitiza (lubiprostone)
- b. Linzess (linaclotide)
- c. Zelnorm (tegaserod)
- d. Metaclopramide
- e. Lotronex (alosetron)
- f. Xifaxan (rifaximin)
- g. Domperidone or Lisopride
- h. Prilosec or other proton-pump inhibitors
- i. Other prescription medications

11. Besides drug therapies, what else are you doing to help reduce your symptoms of functional GI disorders? Check all that apply.

- a. Over-the-counter (such as antispasmodics, pro-motility agents, antidiarrheals)
- b. Dietary management (such as food restrictions or supplementation)
- c. Medical device or surgical treatment (such as feeding tube)
- d. IV therapy (such as total parenteral nutrition (TPN))
- e. Acupuncture or needling
- f. Herbal remedies
- g. Behavioral or psychological therapy
- h. Other, not mentioned
- i. None of the above.

Appendix 4: Incorporating Patient Input into a Benefit-Risk Assessment Framework for Functional GI Disorders

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.⁴ The Benefit-Risk Assessment Framework involves assessing five key decision factors: *Analysis of Condition*, *Current Treatment Options*, *Benefit*, *Risk*, and *Risk Management*. When completed for a particular product, the Framework provides a succinct summary of each decision factor and explains FDA's rationale for its regulatory decision.

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

The input provided by patients and patient representatives through the Functional GI Disorders 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 functional GI disorders below draws from various sources, including what was discussed at the Functional GI Disorders Patient-Focused Drug Development meeting held on May 11, 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 a functional GI disorder. This information is likely to be added to or changed over time based on a further understanding of the condition or changes in the treatment armamentarium.

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

Dimensions	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<p>– Functional gastrointestinal (GI) disorders describes a group of common, chronic GI conditions that affect a part of the GI tract, and are often characterized by chronic time course and unpredictable symptom exacerbations.</p> <p>– Functional GI disorders are highly prevalent and impact across all demographics; approximately two out of five people are affected by a functional GI disorder.</p> <p>– The signs and symptoms vary depending on the specific functional GI disorder. Common signs and symptoms of functional GI disorders relate to abnormal intestinal motility, abnormal intestinal perception, and/or abnormal brain-gut communication. Common symptoms include pain, heartburn, abdominal distention, nausea, vomiting, bloating, constipation, and/or diarrhea. Participants at the Patient-Focused Drug Development meeting identified fatigue (lack of energy, muscle fatigue) and impaired cognitive functioning as symptoms that have a significant impact on daily life.</p> <p>– Functional GI disorders can have significant physical and emotional impact on patients’ quality of life.</p> <p>- <i>See the Voice of the Patient report for a more detailed narrative.</i></p>	<p>Functional GI disorders are a group of chronic conditions with highly variable symptoms that can have a significant impact on patients’ quality of life and over time, it can place a large burden on patients’ ability to live normally.</p>
Current Treatment Options	<p>– Many patients have experimented with a multitude of complex treatment regimens, with varying degree of success.</p> <p>– FDA approved prescription therapies for functional GI disorders include:</p> <ul style="list-style-type: none"> ○ Reglan (metoclopramide) ○ Linzess (linaclotide) ○ Amitiza (lubiprostone) ○ Imodium (loperamide) <p>– Various investigational therapies, off-label prescription, and non-prescription drug therapies are used by practitioners and patients to treat the symptoms of the disease, including domperidone, pain medications, a range of anti-nausea and/or anti-spasm drugs, antibiotics, acid reflux medications, antipsychotics and antidepressants. Non-drug therapies used to help manage symptoms include gastric electrical stimulation, dietary management, acupuncture, massage, heating pads, homeopathic remedies, and chiropractic treatments.</p> <p>- <i>See the Voice of the Patient report for a more detailed narrative.</i></p>	<p>Drug treatments that alleviate or help manage symptoms of functional GI disorders are available; however, efficacy varies from patient to patient, and significant side effects can limit benefits or preclude use of these medications.</p> <p>There is a large unmet need for additional treatments that better target the underlying disease. There is also a continued need for treatments that better manage symptoms without significant side effects or impacts on daily life.</p>