U.S. Food and Drug Administration
Protecting and Promoting Public Health

www.fda.gov

Public Meeting on Patient-Focused Drug Development for Neuropathic Pain Associated with Peripheral Neuropathy

June 10, 2016

U.S. Food and Drug Administration
Protecting and Promoting Public Health

www.fda.gov

Welcome

Soujanya S. Giambone, MBA
Office of Strategic Programs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

June 10, 2016

Agenda

- **Setting the context**
  - Overview of FDA's Patient-Focused Drug Development
  - Background on Neuropathic Pain and Therapeutic Options
  - Road from PFDD Meetings to Clinical Trial Endpoints
  - Overview of Discussion Format
- **Discussion Topic 1**: Disease symptoms and daily impacts that matter most to patients
- **Break**
- **Discussion Topic 2**: Patients' perspectives on current approaches to treatment
- **Open Public Comment**
- **Closing Remarks**

U.S. Food and Drug Administration
Protecting and Promoting Public Health

www.fda.gov

Opening Remarks

Pamela Horn, MD

Medical Officer Team Lead, Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

June 10, 2016

U.S. Food and Drug Administration
Protecting and Promoting Public Health

www.fda.gov

FDA's Patient-Focused Drug Development Initiative

Sara Eggers, PhD
Office of Strategic Programs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

June 10, 2016

Patient-Focused Drug Development under PDUFA V

- **FDA is developing a more systematic way of gathering patient perspective on their condition and available treatment options**
  - Patient perspective helps inform our understanding of the context for the assessment of benefit-risk and decision making for new drugs
  - Input can inform FDA's oversight both during drug development and during our review of a marketing application

- **Patient-Focused Drug Development is part of FDA commitments under the fifth authorization of the Prescription Drug User Fee Act (PDUFA V)**
  - FDA is convening 20+ public meetings on specific disease areas in Fiscal Years 2013-2017
  - Meetings will help develop a systematic approach to gathering patient input

Identifying Disease Areas for the Patient-Focused Meetings

- **FDA announced a preliminary set of diseases as potential meeting candidates**
  - Public input on these nominations was collected. FDA carefully considered these public comments and the perspectives of our drug review divisions at FDA

- **FDA identified a total of 24 diseases to be the focus of meetings for fiscal years 2013-2017**

Disease Areas to be the focus of meetings for FY 2013-2017

Fiscal Year 2013	Fiscal Year 2014	Fiscal Year 2015	Fiscal Year 2016-2017
• Chronic fatigue syndrome/ myalgic encephalomyelitis • HIV • Lung cancer • Narcolepsy	• Sickle cell disease • Fibromyalgia • Pulmonary arterial hypertension • Inborn errors of metabolism • Hemophilia A, B, and other heritable bleeding disorders • Idiopathic pulmonary fibrosis	• Female sexual dysfunction • Breast cancer • Chagas disease • Functional gastrointestinal disorders • Huntington's disease and Parkinson's disease Alpha-1 antitrypsin deficiency	• Non-tuberculous mycobacterial lung infections • Psoriasis • **Neuropathic pain associated with peripheral neuropathy** • Patients who have received an organ transplant (Sept. 27) *To be announced* • Alopecia areata • Autism • Hereditary angioedema • Sarcopenia

Tailoring Each Patient-Focused Meeting

- **Each meeting focuses on a set of questions that aim to elicit patients' perspectives on their disease and on treatment approaches**
  - We start with a set of questions that could apply to any disease area; these questions are taken from FDA's benefit-risk framework and represent important considerations in our decision-making
  - We then further tailor the questions to the disease area of the meeting (e.g., current state of drug development, specific interests of the FDA review division, and the needs of the patient population)
- **Focus on relevant current topics in drug development for the disease at each meeting**
- **We've learned that active patient involvement and participation is key to the success of these meetings.**

"Voice of the Patient" Reports

- Following each meeting, FDA publishes a Voice of the Patient report that summarizes the patient testimony at the meeting, perspectives shared in written docket comments, as well as any unique views provided by those who joined the meeting webcast.

- These reports serve an important function in communicating to both FDA review staff and the regulated industry what improvements patients would most like to see in their daily life.

- FDA believes that the long run impact of this program will be a better, more informed understanding of how we might find ways to develop new treatments for these diseases.

U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

An Overview of Neuropathic Pain Associated with Peripheral Neuropathy

Steven Galati, MD
Division of Anesthesia, Analgesia and Addiction Products (DAAAP)
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

June 10, 2016

Introduction

- Peripheral Neuropathy
  - Caused by damage to the peripheral nerves (nerves outside of the central nervous system)

- Peripheral nerves send information from parts of the body to the brain (e.g., they sense pain)
  - This may be adaptive - will allow us to sense a painful stimulus and respond
  - However, certain conditions may affect the peripheral nerves and cause dysfunction which leads to pain even when a stimulus is not present or an exaggerated response to a stimulus

Introduction cont'd

- Chronic pain conditions are generally divided into several subtypes - nociceptive, neuropathic, or mixed
  - Nociceptive – pain arising from stimulation of nerves due to injury or inflammation from visceral organs (e.g., surgery) or nonvisceral areas (e.g., bone fracture)
  - Neuropathic - pain arising from a lesion or dysfunction within the nervous system
    - **Peripheral** – lesion is within the peripheral nervous system (PNS); nerves outside of the brain and spinal cord

Diagnosis

- Pain is one symptom of peripheral neuropathy and often the main complaint
- Primary physician may initiate work-up/treatment
- Specialists, such as neurology, may be seen treatment is not effective
- Physician may also perform a number of tests in addition to H&P
  - NCV (nerve conduction velocity)
  - EMG (Electromyography)
  - Lab tests (e.g., HIV)
  - Nerve biopsy

Diagnosis cont'd

- Diagnosis is based on a combination of symptoms, history, physical examination and other tests if needed
- Types of Peripheral Neuropathic Pain
  - Painful Diabetic Neuropathy about 10-20% of diabetic patients have pain
  - Postherpetic Neuralgia
  - Complex Regional Pain syndrome
  - HIV-associated Neuropathy
  - Drug-induced Neuropathy (e.g., chemotherapy agents)
  - Alcohol-induced
  - Autoimmune disorders
  - Other infectious (e.g. Lyme disease)
  - Cancers

Symptoms/Manifestation

- Despite numerous causes, the symptoms of peripheral neuropathy are similar and usually include pain
- Common symptoms:
  - Burning sensations
  - Shock like pain
  - Paresthesias/numbness
  - Allodynia (painful sensations to harmless stimuli)
  - Hyperalgesia (increased sensitivity to painful sensations)

Requirements for FDA Approval

- Generally, FDA requires two successful trials for a specific peripheral neuropathic pain condition (e.g., diabetic peripheral neuropathy)
- For a general indication of "treatment of peripheral neuropathic pain" three successful trials in three separate conditions must be completed to ensure efficacy is generalizable

Guidance for Industry, Analgesic Indications: Developing Drug and Biological Products.
http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm384691.pdf

Treatment Options – Drug Therapies

- FDA approved medications:
  - **Diabetic Peripheral Neuropathy (DPN)**:
    - *Nucynta ER* (Tapentadol)
    - *Lyrica* (Pregabalin)
    - *Cymbalta* (Duloxetine)
  - **Postherpetic Neuralgia (PHN)**:
    - *Lyrica* (Pregabalin)
    - *Neurontin* (Gabapentin)
    - *Transdermal lidocaine*
    - *Capsaicin 8% patch*
  - **Trigeminal Neuralgia:**
    - *Tegretol (Carbamazepine)*

Treatment Options – Drug/Biologic Therapies

Strong Recommendation	
Gabapentin (neurontin)	First Line
Pregabalin (lyrica)	First Line
Duloxetine (Cymbalta) or Venlafaxine (Effexor)	First Line
Tricyclic antidepressants (amitriptyline)	First Line
Weak Recommendation	
Patches (capsaicin or lidocaine)	Second Line
Tramadol	Second Line
Opioids	Third Line
Botulinum Toxin A	Third Line

Adapted from the Neuropathic Pain Special Interest Group (NeuPSIG) of the International Association for the Study of Pain revised - The Lancet Neurobiology, Vol. 14, No. 2, pp. 162-173, ***February 2015***

Treatment Options – Drug/Biologic Therapies

- Other agents:
  - Combination treatments (e.g., Lyrica plus Cymbalta)
    - Few trials have shown clear evidence to support use but done in practice
  - Anticonvulsants (valproate, topiramate)
  - IVIG (immunoglobulin)

Treatment Options – Other Components of Therapy

- Treat underlying condition – e.g., tight control of diabetes
- Exercise
  - Shown to improve pain in DPN in some studies
- Cognitive-Behavioral-Therapy (CBT)
- Modalities commonly used but with limited evidence with support from placebo-controlled trials
  - Acupuncture
  - Massage
  - Spinal cord stimulation
  - Transcutaneous Electrical Nerve Stimulation (TENS)

Impact on daily life

- Peripheral neuropathy, and the pain associated with the condition, may have a significant impact of a patient's quality of life
- Key to success is diagnosis, identify and adjust modifiable causes, and maximize effectiveness of treatments while minimizing adverse events
- Peripheral neuropathic pain may be chronic, therefore, a long-term plan to maximize quality of life is important
  - E.g., consider long-term adverse events of treatment

Challenges to Drug Development

- Effectiveness
  - Most patients are not completely satisfied with treatment
  - Most trials compare single agents with a placebo and not multiple modalities which are common in practice
- Is treatment for one type of neuropathy good for another?
  - Many causes of peripheral neuropathy
  - FDA requires studies in multiple types of peripheral neuropathy if company wants their drug indicated for more than one type of PN
- Adverse events
  - Medications may be effective, however, may not be tolerated well or be best option for long-term use

Conclusions

- The FDA is aware of unmet medical needs experienced by patients who have neuropathic pain associated with peripheral neuropathy.

- FDA is conducting this public meeting to obtain input from patients, caregivers, and family members about the impact of neuropathic pain

- Thank you for taking the time to share your comments with us today.

Thank You

References

- Neuropathic Pain Special Interest Group (NeuPSIG) of the International Association for the Study of Pain revised - The Lancet Neurobiology, Vol. 14, No. 2, pp. 162-173, February 2015.
- Baron R, Binder A, Wasner G. Neuropathic pain: diagnosis, pathophysiological mechanisms, and treatment. Lancet Neurol 2010;9:807–19.
- Peripheral Neuropathy:
  - http://www.medscape.com/viewarticle/811592_5
- *Guidance for Industry - Analgesic Indications: Developing Drug and Biological Products*
  - http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm384691.pdf

U.S. Food and Drug Administration
Protecting and Promoting Public Health

www.fda.gov

The Road from PFDD Meetings to Clinical Trial Endpoints

Nikunj B. Patel, Pharm.D
Clinical Outcomes Assessment (COA), Office of New Drugs (OND)
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

June 10, 2016

Disclaimer

The views expressed in this presentation are those of the speaker, and do not necessarily represent an official FDA position.

PATIENT-FOCUSED DRUG DEVELOPMENT (PFDD) MEETINGS

WHERE DO WE GO FROM HERE

PATIENTS' VOICE


I need a valid assessment.

Pathways for FDA Clinical Outcome Assessment Review & Advice

1

IND/NDA/BLA Pathway

Within an individual drug development program

Investigational New Drug (IND) submissions to FDA

Potential to result in *labeling* claims

2

DDT COA Qualification Pathway

Outside of an individual drug development program

Development of novel COAs for use in multiple drug development programs addressing unmet measurement needs

Potential to result in *qualification* of COA

3

Critical Path Innovation Meetings Pathway

Outside of an individual drug development program

Potential for *general CDER advice* on specific methodology or technology (e.g., PRO) in its early stages of development

DDT = Drug Development Tool; COA = Clinical Outcome Assessment; PRO = Patient-Reported Outcome
NDA = New Drug Application; BLA = Biologics Licensing Application

Key Takeaways

- PFDD meetings are a "starting point" for developing & using patient-focused outcome measures and endpoints
- The outcomes of PFDD meetings will support and guide FDA's assessment of clinical benefit in drug reviews
- Patients' input ultimately helps determine:
  - WHAT is measured to provide evidence of treatment benefit
  - HOW best to measure what matters most to patients
  - WHAT amount of change is meaningful to patients

Relevant Resources

- **FDA COA Staff Website:** http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm349031.htm#Endpoints
- **PRO Guidance:** http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf
- **DDT COA Qualification Guidance:** http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM230597.pdf
- **DDT COA Qualification Website:** http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/ucm284077.htm
- **Critical Path Innovation Meeting Website & Guidance:** http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/ucm395888.htm

U.S. Food and Drug Administration
Protecting and Promoting Public Health

www.fda.gov

Overview of Discussion Format

Soujanya S. Giambone
Office of Strategic Programs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

June 10, 2016

Discussion Overview

Topic 1: Disease symptoms and daily impacts

- How would you describe the most bothersome aspect of your neuropathic pain?
- How does your condition affect your ability to do specific activities?
- How your neuropathic pain affects you on the best days? Worst day?
- How has your condition changed over time?
- What worries you most about your condition?

Topic 2: Current approaches to treatment

- What are you doing to treat your neuropathic pain?
- How well is/are the treatment(s) treating your significant symptoms?
- What are the biggest downsides to your treatments?
- What would you look for in an “ideal” treatment?
- What factors do you consider when deciding whether or not to participate in a clinical trial?

Discussion Format

- **We will first hear from a panel of patients**
  - The purpose is to set a good foundation for our discussion
  - They reflect a range of experiences with neuropathic pain

- **We will then broaden the dialogue to include patients in the audience**
  - The purpose is to build on the experiences shared by the panel
  - We will ask questions and invite you to raise your hand to respond
  - Please state your name before answering

Discussion Format, continued

- **You'll have a chance to answer "polling" questions**
  - Their purpose is to aid our discussion
  - In-person participants, use the "clickers" to respond
  - Web participants, answer the questions through the webcast
  - Patients or parents of patients only, please

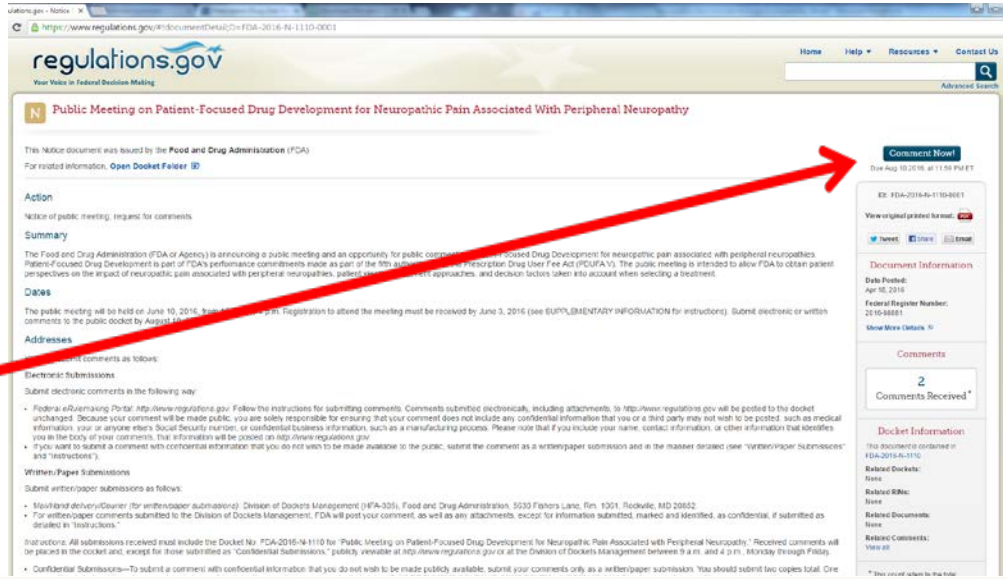
- **Web participants can add comments through the webcast**
  - Although they may not all be read or summarized today, your comments will be incorporated into our summary report
  - We'll occasionally go to the phones to give you another opportunity to contribute

Send us your comments!

- **You can send us comments through the "public docket"**
  - The docket will be open until August 10, 2016
  - Share your experience, or expand upon something discussed today
  - Comments will be incorporated into our summary report
  - Anyone is welcome to comment

Visit:
https://www.regulations.gov/#!documentDetail;D=FDA-2016-N-1110-0001

Click Comment Now!



Resources at FDA

- CDER Office of Center Director
  - Professional Affairs and Stakeholder Engagement (PASE)
  - Contact: Christopher Melton, christopher.melton@fda.hhs.gov
  - Facilitates communication and collaboration between CDER and patient and healthcare professional stakeholders and others on issues concerning drug development, drug review and drug safety.
- FDA Office of Health and Constituent Affairs
  - Contact: PatientNetwork@fda.hhs.gov, (301) 796-8460
  - Liaison between FDA and stakeholder organizations
  - Runs the Patient Representative Program
    - Patient Representatives advise FDA at Advisory Committee meetings

Discussion Ground Rules

- We encourage patients to contribute to the dialogue– caregivers and advocates are welcome too
- FDA is here to listen
- Discussion will focus on symptoms and treatments
  - Open Public Comment Period is available to comment on other topics
- The views expressed today are personal opinions
- Respect for one another is paramount
- Let us know how the meeting went today; evaluation forms are available at the registration table

Where do you live?

A. Within Washington, DC metropolitan area (including the Virginia and Maryland suburbs)
B. Outside of the Washington, D.C. metropolitan area

Have you ever been diagnosed as having neuropathic pain associated with peripheral neuropathy?

A. Yes
B. No

Age?

A. Younger than 18
B. 18 – 29
C. 30 – 39
D. 40 – 49
E. 50 – 59
F. 60 – 69
G. 70 or greater

Do you identify as:

A. Male
B. Female

What is the length of time since your diagnosis of neuropathic pain associated with peripheral neuropathy?

A. Less than 1 year ago
B. 1 years ago to 2 years ago
C. 2 years ago to 5 years ago
D. 5 years go to 10 years ago
E. More than 10 years ago
F. I'm not sure

What is the underlying cause of your neuropathic pain? **Check all that apply**

A. Trauma/physical injury/surgery
B. Metabolic/endocrine disorders (such as diabetes)
C. Medication toxicity (such as chemotherapy drugs, radiation, antiretroviral drugs and other medications)
D. Viral or bacterial infection (such as shingles, herpes, Lyme disease)
E. Other condition not mentioned
F. I'm not sure

What comorbid condition(s) do you have (if applicable)? **Check all that apply.**

A. Depression or anxiety
B. Diabetes
C. Cancer
D. Kidney disease
E. A chronic bacterial or viral infection
F. Other comorbid condition(s) not mentioned
G. I do not have any comorbid conditions that I am aware of

Discussion Topic 1

Disease symptoms and daily impacts that matter most to patients

Soujanya Giambone

Facilitator

Topic 1 Panel Participants

- Susan Waldrop
- Elizabeth Lannon
- Adam Halper
- David Morrow

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

- How would you describe your neuropathic pain associated with peripheral neuropathy? What terms would you use to describe the most bothersome aspects of pain?
- 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?
- How does your neuropathic pain and its negative impacts affect your daily life on the best days? On the worst days?
- How has your neuropathic pain changed over time?
- What worries you most about your condition?

What part(s) of your body do you experience your most severe neuropathic pain? **Check all that apply.**

A. Head, face or neck
B. Hands or arms
C. Feet or legs
D. Trunk
E. Back
F. Genital area
G. Other areas not mentioned

How do your neuropathic pain symptoms typically manifest? **Check all that apply.**

A. Pain appears suddenly and progresses rapidly
B. Pain appears subtly and progresses slowly
C. Pain comes and goes (intermittent)
D. Pain is continuous
E. Pain worsens over time
F. Other manifestation not mentioned
G. I don’t know

What terms best describe the most bothersome aspects of your neuropathic pain? **Please choose up to three terms.**

A. Numbness
B. Tingling
C. Burning
D. Stabbing or shooting pain
E. Prickling/”Pins and needles”
F. Electric shocks
G. Others not mentioned

What are the most bothersome impacts of your neuropathic pain on your daily life? **Please choose up to three impacts.**

A. Ability to participate in or perform activities (such as work, participation in sports or social activities, driving, make or keep plans for activities, etc.)
B. Ability to fall asleep at night
C. Ability to sleep through the night
D. Ability to concentrate or stay focused
E. Ability to care for self, family, and others
F. Impacts on sexual intimacy
G. Emotional impacts (such as fear, hopelessness, etc.)
H. Other impacts not mentioned

BREAK

Discussion Topic 2

Patients' perspectives on current approaches to treatment

Soujanya Giambone
Facilitator

Topic 2 Panel Participants

- Louis Schmitt
- Cherie Pagett
- Linda Spinella
- Jackie Evangelista

Jackie Evangelista

Topic 2 Discussion: Patients' perspectives on current approaches to treatment

- What are you currently doing to help treat your neuropathic pain associated with peripheral neuropathy?
- How well does your current treatment regimen control your condition?
- What are the most significant downsides to your current treatments, and how do they affect your daily life?
- Assuming there is no complete cure for your condition, what specific things would you look for in an ideal treatment for your neuropathic pain?
- If you had the opportunity to consider participating in a clinical trial studying experimental treatments for neuropathic pain, what things would you consider when deciding whether or not to participate?

Have you ever used any of the following drug therapies to help treat your neuropathic pain? **Check all that apply**

A. Antiarrhythmic drugs (such as Mexitil (mexiletine))
B. Antidepressant drugs (such as Elavil (amitriptyline), Prozac (duloxetine), Effexor (venlafaxine))
C. Anticonvulsant drugs (such as Neurontin (gabapentin), Lyrica (pregabalin), Topamax (topiramate), and Tegretol (carbamazepine))
D. Transdermal or topical patches (such as such as lidocaine)
E. Opioid pain medicines
F. Prescription nonsteroidal anti-inflammatory drugs (such as diclofenac)
G. Over-the-counter products (such as ibuprofen and naproxen)
H. Other drug therapies not mentioned
I. I'm not taking any drug therapies

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

A. Surgical destruction of nerves
B. Transcutaneous electrical nerve stimulation (TENS)
C. Cannabinoids (such as medical marijuana)
D. Dietary and herbal supplements
E. Diet modifications and behavioral changes (such as limiting alcohol and tobacco use)
F. Complementary or alternative therapies (such as acupuncture, massage)
G. Physical or occupational therapy
H. Other therapies not mentioned
I. I am not doing or taking any therapies to treat symptoms

Scenario

Imagine that a new medication to treat neuropathic pain associated with peripheral neuropathy has recently been approved by FDA. Your doctor believes that you may be a good candidate for this medication.

In the clinical trials that were conducted, one-half of adults treated for 12 weeks had a 50% reduction in their pain. Common side effects of this medication include: nausea, fatigue, and weight gain. Rare, but serious side effects of this medication include: nerve damage and liver damage.

The medication is unlikely to be addictive or to be used for abuse, such as to get high.

What first thoughts come to mind when hearing this scenario?

What questions would you ask your doctor about this new treatment for neuropathic pain?

Of the following factors, which two would you rank as most important to your decisions about using treatments to help reduce or control your neuropathic pain?

A. How the medication is administered (such as topical, injection, oral, etc.)
B. Your access to this treatment (for example, insurance coverage)
C. Whether the drug showed improvement in specific pain symptoms that are most bothersome to you.
D. The common side effects of the treatment (such as nausea, fatigue, and weight gain)
E. The possibility of rare, but serious side effects (such as nerve and liver damage)
F. The risk of developing drug abuse and addiction
G. Your previous response to a similar treatment
H. Whether you still have other treatment options

Open Public Comment Period

Meghana Chalasani
Office of Strategic Programs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

June 10, 2016

Closing Remarks

Sharon Hertz, MD

Director, DAAAP
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

June 10, 2016