Public Meeting on Patient-Focused Drug Development for Systemic Sclerosis

Tuesday, October 13, 2020

FDA will be streaming a live webcast of the meeting with the presentation slides, which is open to the public at: http://fda.yorkcast.com/webcast/Play/a992e187a44a4b6eafc1aad859153f4d1d. The webcast recording and presentation slides, along with a meeting transcript and summary report, will also be made publicly available after the meeting.

#PFDD
Welcome

Robyn Bent, RN, MS | CAPT, U.S. Public Health Service
Director, Patient-Focused Drug Development Program
Office of Center Director
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Agenda

• Opening Remarks
• Setting the Context
  • Overview of FDA’s Patient-Focused Drug Development Initiative
  • Overview of Systemic Sclerosis
  • Overview of Discussion Format
• Discussion Topic 1: Health Effects and Daily Impacts
• Break
• Discussion Topic 2: Current Approaches to Treatment
• Closing Remarks
Opening Remarks

Nikolay Nikolov, MD
Acting Director
Division of Rheumatology and Transplant Medicine
U.S. Food and Drug Administration
Overview of FDA’s Patient-Focused Drug Development Initiative

Theresa Mullin, PhD
Associate Director for Strategic Initiatives
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
FDA’s role in medical product development and evaluation

FDA’s mission is to **protect and promote public health** by evaluating the **safety and effectiveness of new drugs**.

While FDA plays a critical oversight role in drug development, it is just one part of the process. **FDA does not develop drugs nor conduct clinical trials**.

Review divisions at FDA (e.g., Division of Neurology, Division of Psychiatry, etc.) provide **regulatory oversight** during drug development, make decisions regarding **marketing approval for new drugs**, and **provide guidance** to regulated industry on clinical, scientific and regulatory matters.
What is Patient-Focused Drug Development (PFDD)?

PFDD is a systematic approach to help ensure that patients’ experiences, perspectives, needs, and priorities are captured and meaningfully incorporated into drug development and evaluation.¹

¹https://www.fda.gov/drugs/development-approval-process-drugs/patient-focused-drug-development-glossary
Value of FDA’s PFDD Meetings

- Patients are uniquely positioned to inform FDA understanding of the clinical context for drug review and regulatory decision making
- Prior to PFDD, available mechanisms for obtaining patient input were limited to discussions related to specific applications under review, such as Advisory Committee meetings and only a few patient representatives
- PFDD meetings provide a more systematic way to obtain patients’ perspectives on severity of a condition, and its impact on daily life, and their assessments of available treatment options
PFDD Meetings Provide Key Stakeholders an Opportunity to Hear the Patient’s Voice

The PFDD initiative was established by FDA. FDA values gathering patient input through PFDD meetings. Hosts FDA meetings and attends Externally Led PFDD meetings.

- **2012**: FDA conducted 24 disease-specific PFDD meetings.
- **2013 – 2017**: FDA established Externally Led PFDD meeting option.
- **2017 – Present**:
PFDD meetings in a wide range of disease areas providing insights

<table>
<thead>
<tr>
<th>2013</th>
<th>2014</th>
<th>2015</th>
<th>2016</th>
<th>2017</th>
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<tbody>
<tr>
<td>• Chronic Fatigue Syndrome/Myalgic Encephalomyelitis</td>
<td>• Sickle Cell Disease</td>
<td>• Female Sexual Dysfunction</td>
<td>• Non-Tuberculous Mycobacterial Lung infections</td>
<td>• Sarcopenia</td>
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<td>• HIV</td>
<td>• Fibromyalgia</td>
<td>• Breast Cancer</td>
<td>• Psoriasis</td>
<td>• Autism</td>
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<td>• Lung Cancer</td>
<td>• Pulmonary Arterial Hypertension</td>
<td>• Chagas Disease</td>
<td>• Neuropathic pain associated with peripheral neuropathy</td>
<td>• Alopecia Areata</td>
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<td>• Narcolepsy</td>
<td>• Inborn Errors of Metabolism</td>
<td>• Functional Gastro-intestinal Disorders</td>
<td>• Patients who have received an organ transplant</td>
<td>• Hereditary Angioedema</td>
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<td>• Hemophilia A, B, and other Heritable Bleeding Disorders</td>
<td>• Parkinson’s Disease and Huntington’s Disease</td>
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<td></td>
<td>• Idiopathic Pulmonary Fibrosis</td>
<td>• Alpha-1 Antitrypsin Deficiency</td>
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FDA clinical and statistical review staff have also attended over 28 other Externally-Led PFDD meetings 2016-19 conducted by patient advocacy groups

2018
• Opioid Use Disorder
• Chronic Severe Pain

2020
• Stimulant Use Disorder
PFDD meetings follow a town hall style discussion format

Overview
Clinical Background and Current Available Treatments

Symptoms and Daily Impacts
- Panel of patients and caregivers
- Facilitated group discussion

Current Treatment Options
- Panel of patients and caregivers
- Facilitated group discussion
Each PFDD meeting is tailored to the needs of the specific disease area

• FDA encourages patient advocates, researchers, drug developers, healthcare providers and other government officials to attend PFDD meetings

• However, our focus is on hearing directly from patients and their caregivers, so we ask that others remain silent in listening mode during the discussions since the meetings are a platform to hear directly from patients, caregivers and patient representatives.

• After the PFDD meeting, a Voice of the Patient report summarizes the input shared by patients and caregivers.
Thank you!
An Overview of Systemic Sclerosis

Dinesh Khanna, MBBS, MSc
Michigan Medicine Rheumatology Clinic | Taubman Center
Michigan Medicine
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Systemic Sclerosis

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Public Meeting on Patient-Focused Drug Development for Systemic Sclerosis
Disclosures

• Grant support: Bayer, BMS, Pfizer, NIH/NIAID, NIH/NIAMS, Immune Tolerance Network, Horizon

• Consultant for clinical trial design or funding of an investigator-initiated trial:
  – Acceleron
  – Actelion
  – Abbvie
  – Amgen
  – Bayer
  – Boehringer-Ingelheim
  – CSL Behring
  – Corbus
  – Gilead
  – Galapagos
  – Genentech/Roche
  – GSK
  – Horizon
  – Merck
  – Mitsubishi Tanabe Pharma
  – Sanofi-Aventis/Genzyme
  – United Therapeutics

• Stocks
  – Eicos Sciences, Inc.

• No promotional talk
The word “scleroderma” comes from two Greek words: “sclero” meaning hard, and “derma” meaning skin.

- There are approximately 200,000 patients in the US.
- Approximately 75,000-80,000 have systemic sclerosis (SSc).
Many faces of SSc
Pathogenesis of SSc

Environmental trigger, genetics/epigenetics
SSc—Epidemiology

- Peak age 30-50 yrs
- Female predominance of 3-5:1
- Rare disease
  - Estimated prevalence
    - US $276/10^6$
    - Europe $88-160/10^6$
  - Estimated incidence 18.7 cases/ million/ year
  - With US population as ~ 328 million people, there are ~ 6,000 new SSc cases diagnosed each year
- Heterogeneous disease
- High morbidity and highest mortality among rheumatic diseases

1) Chifflow H Semin Arthritis Rheum 37:223-235
3) Steen V Ann Rheum Dis 2007
### 2013 ACR/EULAR Classification Criteria For SSc

<table>
<thead>
<tr>
<th>Criteria Domain</th>
<th>Sub-Criteria</th>
<th>Weight</th>
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<tbody>
<tr>
<td>Skin thickening of fingers (count higher of the 2)</td>
<td>Puffy fingers</td>
<td>2</td>
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<tr>
<td></td>
<td>Whole finger, distal to metacarpophalangeal joint</td>
<td>4</td>
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<tr>
<td>Finger tip lesions (count higher of the 2)</td>
<td>Digital tip ulcers</td>
<td>2</td>
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<tr>
<td></td>
<td>Pitting ulcers</td>
<td>3</td>
</tr>
<tr>
<td>Abnormal nailfold capillaries</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Telangiectasia</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Lung involvement</td>
<td>Pulmonary arterial hypertension/interstitial lung disease</td>
<td>2</td>
</tr>
<tr>
<td>Raynaud’s phenomenon</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>Scleroderma-associated antibodies</td>
<td>ACA, Anti-SCL-70, Anti-RNA polymerase III</td>
<td>3</td>
</tr>
<tr>
<td>TOTAL SCORE of 9 or more as classified as SSc</td>
<td></td>
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Limited and Diffuse SSc

60% Limited

40% Diffuse

5-10% with sine and overlap disease

Medsger T. In Clements and Furst 2nd Edition, Systemic Sclerosis
Usual Timing of Problems in Systemic Sclerosis

2-5 years after first non RP symptom/sign

SKIN THICKNESS

TIME

LIMITED CUTANEOUS VARIANT

interstitial lung disease

Raynaud, digital ischemia

tendon/bursal friction rubs; joint contractures

esophageal disease

interstitial lung disease

myocardial involvement

“renal crisis”

pulmonary hypertension

malabsorption

Limited

Diffuse

DIFFUSE CUTANEOUS VARIANT

skeletal myopathy

pulmonary hypertension
Diffuse vs Limited Scleroderma - Distinguishing Features -

**Diffuse**
- Heart (severe in 10%)
- Kidney (severe in 15-20%)
- Pulmonary arterial hypertension (5-10%)
- Large joint contractures
- Reduced survival due to more severe internal organ involvement

**Limited**
- Minimal heart
- Minimal kidney
- Pulmonary arterial hypertension (10-15%)
- Late: Primary biliary cirrhosis (<5%)
Autoantibody and Molecular Subsets

Target antigen
- Centromere
- Topoisomerase-1 (Scl70)
- RNA polymerase III
- Fibrillarin (U3RNP)
- Pm-Scl

Fibroproliferative
Inflammatory
Limited
Normal-like
Clinician Viewpoint

- Vasodilators

Screen and Treat early

- Screen for early organ involvement
- Prevent internal organ involvement (if possible)
- Reduce disability
- Decrease progressive disease in the heart, lungs, and other organ

- Immunosuppressive medications
- Anti-fibrotic therapies
- Stem cell transplant
Patient Journey
Patient’s own illustration depicting their experience of skin symptoms of SSc

"Feels like this] all the time… right now I could have that mask on."

"Stretched out of shape… especially over my chest, lungs not expanding. Of my body this bit [chest/body] are the tightest."

Khanna D, et al. Journal of Scleroderma and Related Disorders 2020

Patient verbatim from interview
The patient journey with early SSc from initial symptoms to progressive disease

Initial symptoms
- Skin thickening
- Raynaud’s phenomenon
- Swelling of hands
- Fatigue
- Pain

Diagnosis
- Delays reaching appropriate specialist
- Shock at severity of disease
- Poor prognosis

Treatment
- High treatment burden
- Limited options
- No cure

Worsening symptoms
- Loss of mobility/dexterity
- Pain
- Exhaustion
- Changed appearance
- Depression/anxiety
- Worry about organ involvement

Khanna D, et al. Journal of Scleroderma and Related Disorders 2020
Recent trials-Lessons Learned

- Finding people with SSc for the trials
  - Difficult in an orphan disease
- Lack of expertise outside scleroderma community
- Marked heterogeneity in outcome measures
- Lack of patients’ voice as primary approvable endpoints
Overview of Discussion
Format

Robyn Bent, RN, MS | CAPT, U.S. Public Health Service
Director, Patient-Focused Drug Development Program
Office of Center Director
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Discussion Overview

**Topic 1: Health Effects and Daily Impacts That Matter Most to Patients**
- Health effects of systemic sclerosis that have the most significant impact on your daily life
- How your systemic sclerosis has changed over time
- What worries you most about your systemic sclerosis

**Topic 2: Current Approaches to Treatment**
- Your experience with treating your systemic sclerosis
- What approaches you use to treat your systemic sclerosis
- What you have found to be most effective in helping you treat your systemic sclerosis
- What factors you would consider when considering or seeking treatment
Discussion Format, continued

You will have a chance to answer polling questions

• Their purpose is to aid our discussion
• Participants can use the mentimeter.com link to answer polling questions
• Individuals or family members only, please

Participants can add comments through the webcast or by telephone

• Although they may not all be read or summarized today, your comments will be incorporated into our summary report
Send us your comments!

You can send us comments through the “public docket”

- The docket will be open until December 15, 2020
- Comments will be incorporated into our summary report
- Anyone is welcome to comment

Visit:

Or Search “patient-focused systemic sclerosis” on
www.regulations.gov

And Click Comment Now!
Discussion Ground Rules

• We encourage all individuals and family members to contribute to the dialogue
• FDA is here to listen
• Discussion will focus on systemic sclerosis health effects and treatment
• The views expressed today are personal opinions
• Respect for one another is paramount
Do you live in the Washington, D.C. metropolitan area (including the Virginia and Maryland suburbs)?

a. Yes
b. No

Participation in the polling questions is voluntary. The results are used as a discussion aid only and should not be considered scientific data.

www.fda.gov
Do you live in the Washington, D.C. metropolitan area (including the Virginia and Maryland suburbs)?

- Yes: 4
- No: 48
Have you or your loved one ever been diagnosed as having systemic sclerosis?

a. Yes
b. No

Participation in the polling questions is voluntary. The results are used as a discussion aid only and should not be considered scientific data.
Have you or your loved one ever been diagnosed as having systemic sclerosis?
What is you/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

Participation in the polling questions is voluntary. The results are used as a discussion aid only and should not be considered scientific data.
What is your age?

- Younger than 18: 0
- 18 - 30: 1
- 31 - 40: 7
- 41 - 50: 11
- 51 - 60: 14
- 61 - 70: 5
- 71 or greater: 2
Do you/your loved one identify as:

a. Female
b. Male
c. Other

Participation in the polling questions is voluntary. The results are used as a discussion aid only and should not be considered scientific data.
Do you identify as:

- Female: 32
- Male: 8
- Other: 1
What is the length of time since your diagnosis?

a. Less than 1 year ago
b. 1 years ago to 5 years ago
c. 5 years ago to 10 years ago
d. More than 10 years ago
e. I’m not sure

Participation in the polling questions is voluntary. The results are used as a discussion aid only and should not be considered scientific data.
What is the length of time since your diagnosis?

- Less than 1 year ago: 2
- 1 year ago to 5 years ago: 7
- 5 years ago to 10 years ago: 4
- More than 10 years ago: 19
- I'm not sure: 1
Which subtype of systemic sclerosis have you been diagnosed with? **Select all that apply.**

a. Diffuse  
b. Limited  
c. Sine  
d. Systemic sclerosis with overlap syndrome  
e. Other  
f. I’m not sure

Participation in the polling questions is voluntary. The results are used as a discussion aid only and should not be considered scientific data.
Which subtype of systemic sclerosis have you been diagnosed with? Select all that apply.

- Diffuse: 15
- Limited: 13
- Sine: 1
- Systemic sclerosis with overlap syndrome: 9
- Other: 0
- I’m not sure: 2
Discussion Topic 1
Health Effects and Daily Impacts of Systemic Sclerosis
Topic 1 Discussion Questions

1. Which aspects of systemic sclerosis have the most significant impact on your life?

2. Are there specific activities that are important to you but that you cannot do at all or as fully as you would like because of your systemic sclerosis?
   a. How does your systemic sclerosis and its impacts affect your daily life on the best days?
   b. On the worst days?

3. How has your systemic sclerosis changed over time?
   a. How long have you had symptoms and how long has it been since you were diagnosed with scleroderma?
   b. Would you define your systemic sclerosis today as being well-managed?

4. What worries you most about your systemic sclerosis?

5. If you could change one thing about your systemic sclerosis, what would it be?
Of all the symptoms you have experienced because of your systemic sclerosis, which do you consider to have the most significant impact on your daily life? Please choose up to three symptoms.

a. Hardening or tightening of patches of skin  
b. Skin thickening  
c. Digital ulcers  
d. Raynaud’s phenomenon  
e. Heartburn  
f. Digestive symptoms  
g. Arthritis  
h. Fatigue  
i. Other

Participation in the polling questions is voluntary. The results are used as a discussion aid only and should not be considered scientific data.
Of all the symptoms you experienced because of your systemic sclerosis, which have the most significant impact on your daily life?
Of all the symptoms you have experienced because of your systemic sclerosis, which single symptom do you consider to be most bothersome?

a. Hardening or tightening of patches of skin  
b. Skin thickening  
c. Digital ulcers  
d. Raynaud’s phenomenon  
e. Heartburn  
f. Digestive symptoms  
g. Arthritis  
h. Fatigue  
i. Other

Participation in the polling questions is voluntary. The results are used as a discussion aid only and should not be considered scientific data.
Of all the symptoms you have experienced because of your systemic sclerosis, which single symptom do you consider to be most bothersome?
Which aspects of daily functioning or movement are most affected by your systemic sclerosis? Please choose up to three answers.

a. Ability to sleep
b. Ability to move hands and fingers
c. Ability to walk
d. Ability to breathe
e. Ability to eat
f. Ability to complete household tasks
g. Ability to complete professional/work tasks
h. Emotional or psychological impacts
i. Other impacts not mentioned

Participation in the polling questions is voluntary. The results are used as a discussion aid only and should not be considered scientific data.
Which aspects of daily functioning or movement are most affected by your systemic sclerosis?

- Ability to sleep: 8%
- Ability to move hands and fingers: 8%
- Ability to walk: 8%
- Ability to breathe: 15%
- Ability to eat: 8%
- Ability to complete household tasks: 8%
- Ability to complete professional/work tasks: 8%
- Emotional or psychological impacts: 15%
- Other impacts not mentioned: 23%
Send us your comments!

You can send us comments through the “public docket”

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Or Search “patient-focused systemic sclerosis” on www.regulations.gov

And Click Comment Now!
Discussion Topic 2

Current Approaches to Treatment
Topic 2 Discussion Questions

1. What are you currently doing to help treat your systemic sclerosis?
   a. How has your treatment regimen changed over time, and why?
   b. What symptom would you most like to be improved or resolved by treatment?

2. How well does your current treatment regimen treat the most significant aspects of your systemic sclerosis?

3. What are the most significant downsides to your current treatments, and how do they affect your daily life?

4. Aside from a complete cure for your systemic sclerosis, what specific things would you look for in an ideal treatment for your systemic sclerosis?

5. What factors do you consider when making decisions about selecting a course of treatment?

6. Efficacy and safety are important for any treatment. When you think about a treatment for your disease:
   a. Does it make a difference whether:
      i. the product might improve your most bothersome symptoms or
      ii. whether the product might preserve organ function, or
      iii. would you consider improvement in either of those areas equally worth the same level of risk?
   b. Does your acceptance of potential safety risks go up with the potential effectiveness of a product?
      i. What degree of risk are you willing to accept for an effective treatment? Risks associated may range from mild to severe and life-long (such as life-long immunosuppression, risk of potential cancer associated with treatment).
      ii. If you had to choose between two products, which would you prefer? A very safe product that works somewhat, or a less safe product that works really well?

www.fda.gov
Have you ever used any of the following interventions or medical products (drug therapies or medical devices) to treat your systemic sclerosis? Check all that apply.

a. Medications to modify blood flow (such as nifedipine)
b. Medications to prevent organ rejection and/or treat arthritis (such as Cyclosporine, Azathioprine)
c. Antifibrotic medications for interstitial lung disease (such as nintedanib)
d. Corticosteroids for skin and arthritis symptoms (such as prednisone)
e. Proton-pump inhibitors for digestive symptoms (such as omeprazole)
f. Painkillers (such as Vicodin, Percocet, OxyContin)
g. Bone marrow or solid organ transplant
h. Other
i. I’m not using any medical products or interventions

Participation in the polling questions is voluntary. The results are used as a discussion aid only and should not be considered scientific data.
Have you ever used any of the following interventions or medical products (drug therapies or medical devices) to treat your systemic sclerosis?

- Medications to modify blood flow (such as nifedipine): 20%
- Medications to prevent organ rejection and/or treat arthritis (such as Cyclosporine, Azathioprine): 9%
- Antifibrotic medications for interstitial lung disease (such as nintedanib): 5%
- Corticosteroids for skin and arthritis symptoms (such as prednisone): 17%
- Proton-pump inhibitors for digestive symptoms (such as omeprazole): 21%
- Painkillers (such as Vicodin, Percocet): 15%
- Bone marrow or solid organ transplant: 0%
- Other: 15%
- I'm not using any medical products or interventions: 0%
Besides the medical products or interventions mentioned previously, what else are you doing to manage your systemic sclerosis? **Check all that apply.**

a. Over the counter medications
b. Moisturizers
c. Physical therapy and exercise
d. Diet modifications
e. Counseling or psychological treatment
f. Other therapies not mentioned
g. I am not doing or taking any therapies to manage my systemic sclerosis

Participation in the polling questions is voluntary. The results are used as a discussion aid only and should not be considered scientific data.
Besides the medical products or interventions mentioned previously, what else are you doing to manage your systemic sclerosis?

- Over the counter medications: 19%
- Moisturizers: 23%
- Physical therapy and exercise: 20%
- Diet modifications: 21%
- Counselling or psychological treatment: 7%
- Other therapies not mentioned: 11%
- I am not doing or taking any therapies to manage my systemic sclerosis: 0%
For the medical products or interventions you use, what about the treatment bothers you the most? **Please choose up to three answers.**

a. How the medication is administered  
b. The treatment only provides minimal benefit  
c. The treatment is effective only for a short-term  
d. Bothersome side effects of the treatment  
e. Concern about serious risks of the treatment  
f. Uncertainty about long-terms effects of treatment  
g. Difficulty in accessing treatment  
h. Other negative impacts not mentioned

Participation in the polling questions is voluntary. The results are used as a discussion aid only and should not be considered scientific data.
For the medical products or interventions you use, what about the treatment bothers you the most?

- How the medication is administered: 6%
- The treatment only provides minimal benefit: 19%
- The treatment is effective only for a short-term: 8%
- Bothersome side effects of the treatment: 15%
- Concern about serious risks of the treatment: 21%
- Uncertainty about long-term effects of treatment: 17%
- Other negative impacts not mentioned: 6%
Imagine that a new self-injectable medication indicated to treat systemic sclerosis 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, the medication was shown to reduce the symptom that most significantly impacts your daily life when injected once weekly.

More common side effects of this therapy may include headache, diarrhea, nausea, stomach or abdominal pain, and weight loss. Rarer but more serious side effects may include infection, seizures, trouble breathing, fever, general feeling of discomfort or illness, and risk of bleeding.

Given the risks and benefits, would you take this medication?

a. Yes
b. No
c. Maybe

Participation in the polling questions is voluntary. The results are used as a discussion aid only and should not be considered scientific data.
Given the risks and benefits, would you take this medication?
Send us your comments!

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And Click Comment Now!
Closing Remarks

Raj Nair, MD
Medical Officer
Division of Rheumatology and Transplant Medicine
U.S. Food and Drug Administration