Patient Experience Data: Use in Regulatory Decision Making and Labeling

14th Annual
Patient-Reported Outcome Consortium Workshop

April 19-20, 2023 • Silver Spring, MD

CRITICAL PATH INSTITUTE

Disclaimer

- The views and opinions expressed in the following slides are those of the individual presenters and should not be attributed to their respective organizations/companies, the U.S. Food and Drug Administration or the Critical Path Institute.
- These slides are the intellectual property of the individual presenters and are protected under the copyright laws of the United States of America and other countries. Used by permission. All rights reserved. All trademarks are the property of their respective owners.

Session Objectives

- Define patient experience data (PED)
- Dispel myths, misconceptions, and misunderstandings about PED
- Discuss examples of use in FDA regulatory decision making and labeling
- Present case studies in dermatology and gastroenterology to highlight different approaches to collecting PED from patient advocacy group perspective

Session Participants

Moderator

- *Sonya Eremenco, MA* – Executive Director, Patient-Reported Outcome Consortium, Critical Path Institute

Presenters and Panelists

- *Robyn Bent, RN, MS* – Director, Patient-Focused Drug Development Program, Center for Drug Evaluation and Research, U.S. Food and Drug Administration
- *Michelle Campbell, PhD* – Associate Director for Stakeholder Engagement and Clinical Outcomes, Office of Neuroscience, Office of New Drugs, Center for Drug Evaluation and Research, U.S. Food and Drug Administration
- *Ellyn Kodroff, BS* – President and Founder, CURED (Campaign Urging Research for Eosinophilic Diseases)
- *Sarrit Kovacs, PhD* – Clinical Reviewer, Division of Gastroenterology (DG), Office of Immunology and Inflammation (OII), Office of New Drugs (OND), Center for Drug Evaluation and Research (CDER), U.S. Food and Drug Administration (FDA)
- *Marc Yale* – Advocacy and Research Coordinator, International Pemphigus Pemphigoid Foundation (IPPF)

Patient Experience Data

April 2023

Robyn Bent, RN, MS
Director, Patient-Focused Drug Development Program
Center for Drug Evaluation and Research (CDER)

CDER Patient-Focused Drug Development (PFDD)

- Establishing the therapeutic context is an important aspect of benefit-risk assessment
  - Patients are uniquely positioned to inform understanding of this context
- 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
- PFDD efforts include:
  - FDA-led PFDD Meetings
  - Externally-led PFDD Meetings
  - PFDD Methodological Guidance Series
  - Clinical Outcome Assessment (COA) Grant Program

https://www.fda.gov/drugs/development-approval-process-drugs/cder-patient-focused-drug-development

Supposing is good, but finding out is better

……..Mark Twain

What is Patient Experience Data?

Patient experience data include the experiences, perspectives, needs, and priorities of patients related to:

- The signs and symptoms patients experience and how these signs and symptoms affect their day-to-day functioning and quality of life
- The course of their disease over time, including the effect the disease has on patients' day-to-day function and quality of life over time, and the changes that patients experience in their symptoms over time
- Patients' experience with the treatments for their disease: the symptoms and burdens related to treatment
- Patients' views on potential disease or treatment outcomes and how they weigh the importance of different possible outcomes
- How patients view the impact of the disease, treatment, and outcomes, and their view of potential tradeoffs between disease outcomes and treatment benefits and risks

Parts of the patient experience to collect and/or measure

These may include:

- Impact of the disease and its treatment on the patient
  - Signs/symptoms of disease or condition
  - Chief complaints (most bothersome signs/symptoms)
  - Burden of living with or managing a disease or condition (including effect of the disease or condition on activities of daily living and functioning)
  - Burden of treatment (including the effect of treatment on activities of daily living and functioning)
  - Burden of participating in clinical studies

Parts of the patient experience to collect and/or measure (cont.)

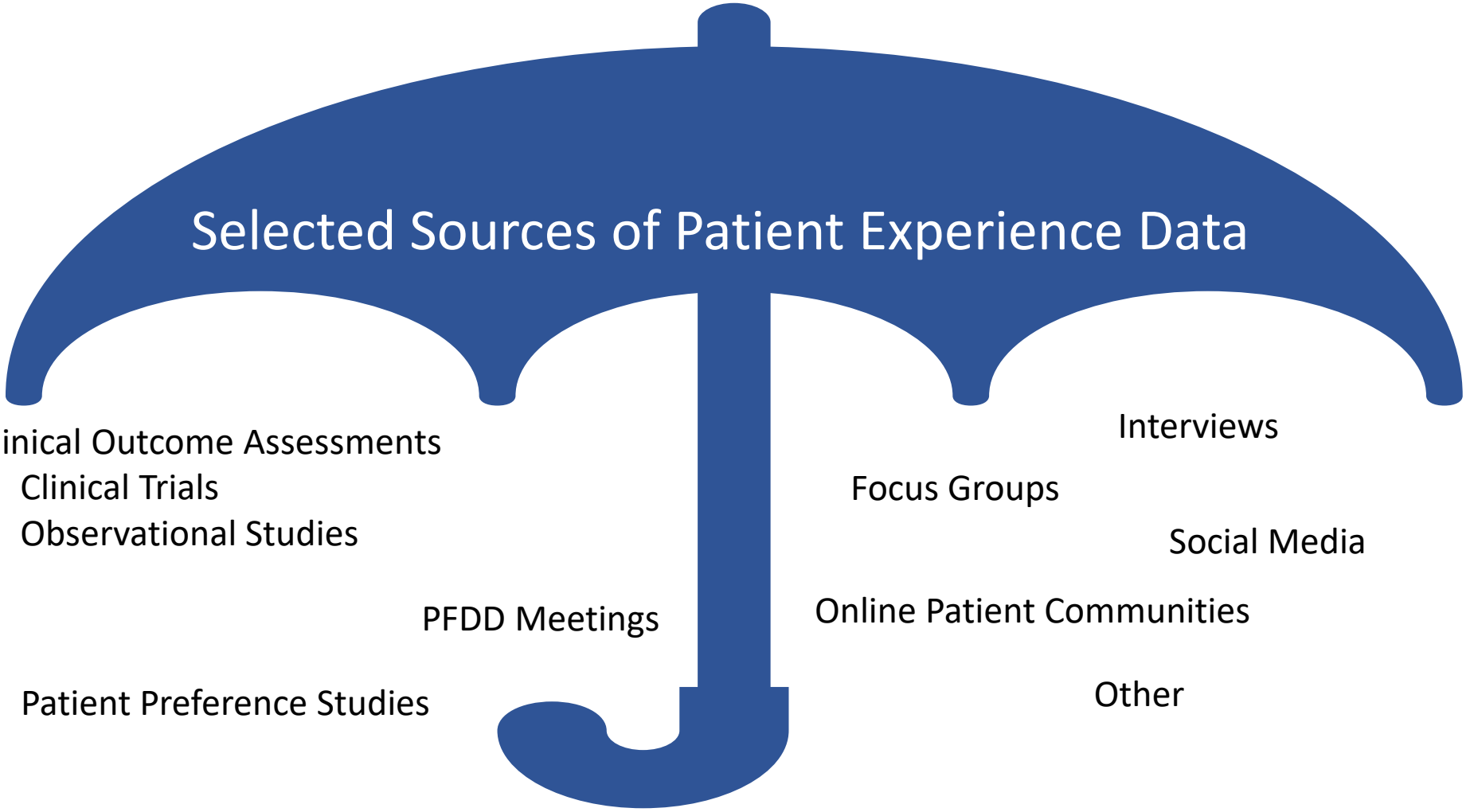
These may include:

- Patients' perspectives about potential and current treatments
  - Expectations of benefits
  - Tolerance for harms or risks
  - Acceptable tradeoffs of benefits and risks (i.e., patient preference)
  - Attitudes towards uncertainty
- Views on unmet medical needs and available treatment options
- Enhanced understanding of the natural history of the disease or condition, including progression, severity, and chronicity

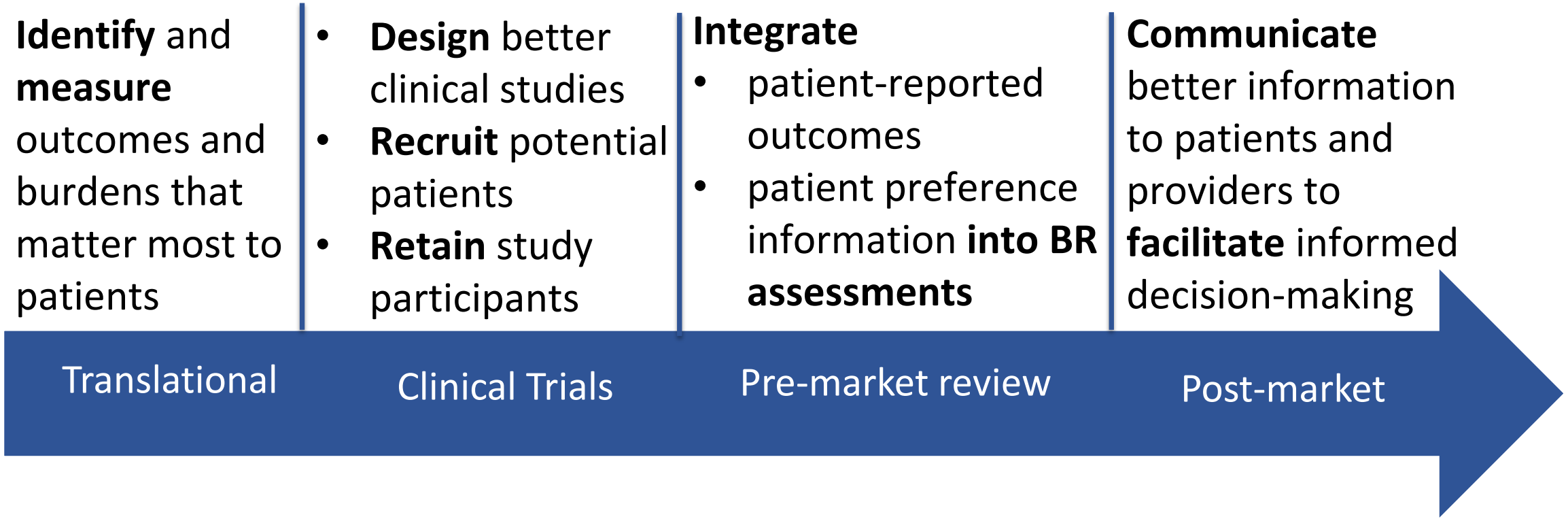
When and how to collect Patient Experience Data

- Patient experience data may be collected throughout medical product development
  - beginning at the launch of a discovery program
  - independent of any specific medical product development program
- Depending on study or research goals and the research questions, qualitative, quantitative, or mixed methods may be appropriate for collection of patient experience data

Selected Sources of Patient Experience Data



Integrating patient input into medical product development and decision making



Need to build in patient input starting in the translational phase

Patient-Focused Drug Development Meetings

- Which **symptoms have the most significant impact** on a patient's daily life?... On their ability to do specific activities?
- How well does their **current treatment regimen** treat the most significant symptoms of their disease or condition?
- What specific things would they look for in an **ideal treatment** for their condition?
- What **factors do they take into account when making decisions** about using treatments? …. Deciding whether to **participate in a clinical trial**?

Each meeting results in a **Voice of the Patient report** that faithfully captures patient input

Patient Experience Data

April 2023

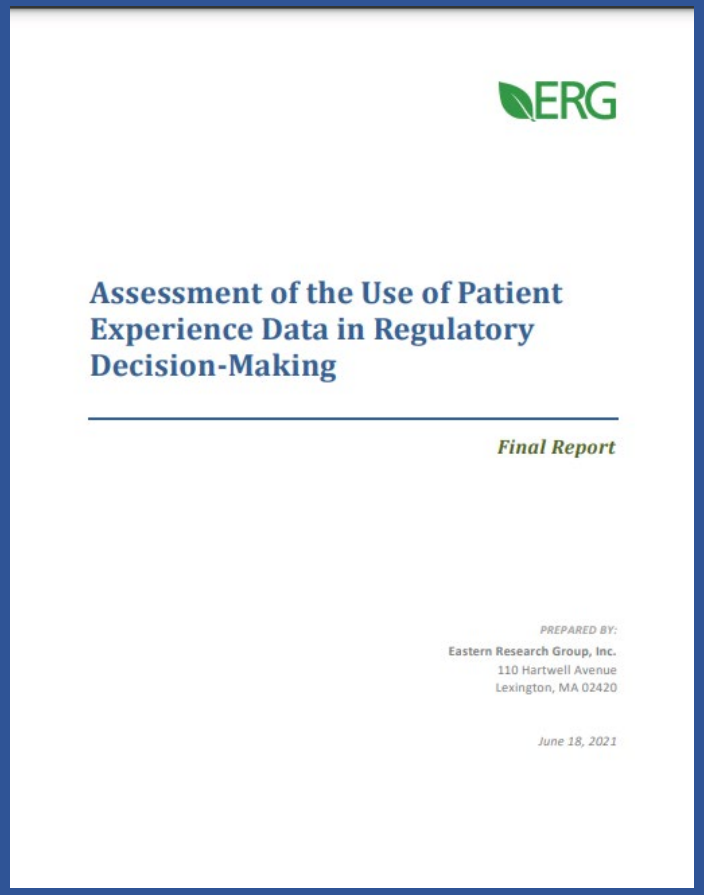
Michelle Campbell, PhD
Associate Director, Stakeholder Engagement and Clinical Outcomes
Office of Neuroscience (ON), Center for Drug Evaluation and Research (CDER)

Patient Experience Data?

Patient experience data has been incorporated in regulatory review for many years prior to 21st Century Cures acknowledgment

- Prior to December 2016
  - Disease-specific guidances
  - 2009 PRO Guidance
  - PFDD Program

Solidifies the importance of capturing patients' lived experiences through a spectrum of opportunities



FDA

Table 2-3. Types of patient experience data mentioned in FDA reviews

Metric	FDA Reviews that Contain PED for Approved NME NDAs and BLAs (n=120)
Of FDA reviews that mention patient experience data, percent that mention data from **applicants**	97%
• PRO	84%
• ClinRO	33%
• PerfO	9%
• ObsRO	7%
• Patient preference study	3%
Of FDA reviews that mention patient experience data, percent that mention data from **other sources**	11%
• PFDD meetings	4%
• Natural history study	3%

PED = Patient Experience Data. PRO = Patient-Reported Outcome. ClinRO = Clinician-Reported Outcome. PerfO = Performance Outcome. ObsRO = Observer-Reported Outcome.

*NME NDAs and BLAs received by FDA between June 12, 2017 and June 12, 2020, and approved by CDER or CBER by February 5, 2021.

**Percentages sum to more than 100% because some review documents mention patient experience data from both the application and other sources.

Patient Experience Data Table

Patient Experience Data Relevant to this Application (check all that apply)

				Section of review where discussed, if applicable
☐	**The patient experience data that were submitted as part of the application include:**			
	☐	Clinical outcome assessment (COA) data, such as		
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
	Patient experience data was not submitted as part of this application.			

Examples in Reviews

NDA Multi-disciplinary Review and Evaluation – NDA 210361
QBREXZA (glycopyrronium) cloth, 2.4%

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

X	The patient experience data that was submitted as part of the application include:			Section where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as		
		X	Patient reported outcome (PRO)	Section 7.2 Study endpoints (7.2.1, 7.2.5)
		□	Observer reported outcome (ObsRO)	
		X	Clinician reported outcome (ClinRO)	Section 7.4.5.2, Local Skin Reactions
		□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		
	□	Patient preference studies (e.g., submitted studies or scientific publications)		
	X	Other: (Please specify)		References/publications examining patient experience; discussed in Section 2.1
X	Patient experience data that were not submitted in the application, but were considered in this review:			
		X	Input informed from participation in meetings with patient stakeholders	Sections 2.1 and 7.2 – input from PFDD meeting 11/13/17
		□	Patient-focused drug development or other stakeholder meeting summary reports	
		□	Observational survey studies designed to capture patient experience data	
		□	Other: (Please specify)	
□	Patient experience data was not submitted as part of this application.			

2.1. Analysis of Condition

Hyperhidrosis is a condition of excessive sweating beyond what is physiologically required to regulate normal body temperature. Hyperhidrosis is most often a primary, idiopathic condition; however, a number of disorders, including endocrine, neurologic, cardiovascular and metabolic conditions, and a number of medications, can cause secondary hyperhidrosis.

Primary hyperhidrosis is generally localized and symmetric, most often affecting the axillae, palms and soles, though it can also involve the face, scalp, trunk and intertriginous areas. The diagnosis is clinical. Symptoms generally start in late childhood or adolescence, following puberty, and may persist throughout life or spontaneously remit with age. Estimates of prevalence in the US range from 1 to 5 percent of the population[1]. A 2016 survey estimated the prevalence of hyperhidrosis at 4.8 %, which represents approximately 15.3 million people in the United States[2]. Though the pathophysiology of primary hyperhidrosis is not completely understood, the sweat glands are generally histologically and functionally normal; rather, excessive sweating in primary hyperhidrosis appears to be an exaggerated central (cortical) response to normal emotional stress[1].

A study examining Canadian and Chinese dermatology patients found that the prevalence of anxiety and depression was 21.3% and 27.2% in patients with hyperhidrosis, and 7.5% and 9.7% in patients without hyperhidrosis, respectively[3]. Increased severity of hyperhidrosis was also correlated with higher rates of anxiety and depression.

The impact of hyperhidrosis on the daily lives of patients was among the topics discussed at an external Patient-Focused Drug Development Meeting for hyperhidrosis held on November 13, 2017. Patients who attended the meeting described the effects of the condition on their quality of life, as well as the patient experience with the available treatment modalities. The final summary report of the meeting is expected to be published in the second-half of 2018.

Examples in Reviews

NDA 217026
DAYBUE (Trofinetide)

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☒	The patient experience data that was submitted as part of the application include:			Section where discussed, if applicable
	☒	Clinical outcome assessment (COA) data, such as		Sec 6.1 Study endpoints
		☐	Patient reported outcome (PRO)	
		☒	Observer reported outcome (ObsRO)	Sec 6.1 Study endpoints
		☒	Clinician reported outcome (ClinRO)	Sec 6.1 Study endpoints
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify)		
☒	Patient experience data that were not submitted in the application, but were considered in this review:			
		☐	Input informed from participation in meetings with patient stakeholders	
		☒	Patient-focused drug development or other stakeholder meeting summary reports	Sec 2 Therapeutic Context
		☐	Observational survey studies designed to capture patient experience data	
		☐	Other: (Please specify)	
☐	Patient experience data was not submitted as part of this application.			

An externally-led Patient Focused Drug Development meeting was co-hosted by the International Rett syndrome Foundation and the Rett syndrome Research Trust on March 11, 2022. A Voice of the Patient report was published August 9, 2022, based on the content of this meeting and online comments submitted afterward (Coenraads, Hehn et al. 2022). This meeting emphasized the diverse array of dynamic symptoms that make living with Rett syndrome difficult for both patients and caregivers. The inability to communicate was identified as the top area of concern, as Rett patients appeared to their caregivers to be cognitively aware and distressed by their communication impairments. Patients and caregivers expressed a dire unmet therapeutic need for treatments that directly address Rett syndrome and to improve communication and hand use. They also expressed a willingness to try anything to lessen the suffering of patients with Rett syndrome. In conclusion, Rett syndrome is a serious condition with unmet medical need.

Labeling of Patient Experience Data

- Still have to follow regulatory requirements for inclusion in labeling
  - Includes:
    - Rigor
    - Early discussions with the review divisions
  - PFDD Guidance Series should be utilized

Upcoming Webinar

https://www.fda.gov/drugs/news-events-human-drugs/public-webinar-patient-focused-drug-development-incorporating-clinical-outcome-assessments-endpoints

VIRTUAL

Public Webinar Patient-Focused Drug Development: Incorporating Clinical Outcome Assessments into Endpoints for Regulatory Decision Making – Draft Guidance

MAY 4, 2023

Share | Tweet | LinkedIn | Email | Print

On This Page

- Meeting Information

Date: May 4, 2023

Time: 1:00 PM - 3:00 PM ET

Attend

Register for This Event

On May 4, 2023, the U.S. Food and Drug Administration (FDA) is hosting a webinar for patients, industry, and other interested stakeholders to discuss and answer questions about the draft guidance: Patient-Focused Drug Development: Incorporating Clinical Outcome Assessments into Endpoints for Regulatory Decision Making.


FDA
U.S. FOOD & DRUG
ADMINISTRATION

Patient Journey to the First FDA-approved Drug for Eosinophilic Esophagitis

Ellyn Kodroff,
President and Founder,
CURED (Campaign Urging Research for Eosinophilic Diseases)

CURED Foundation

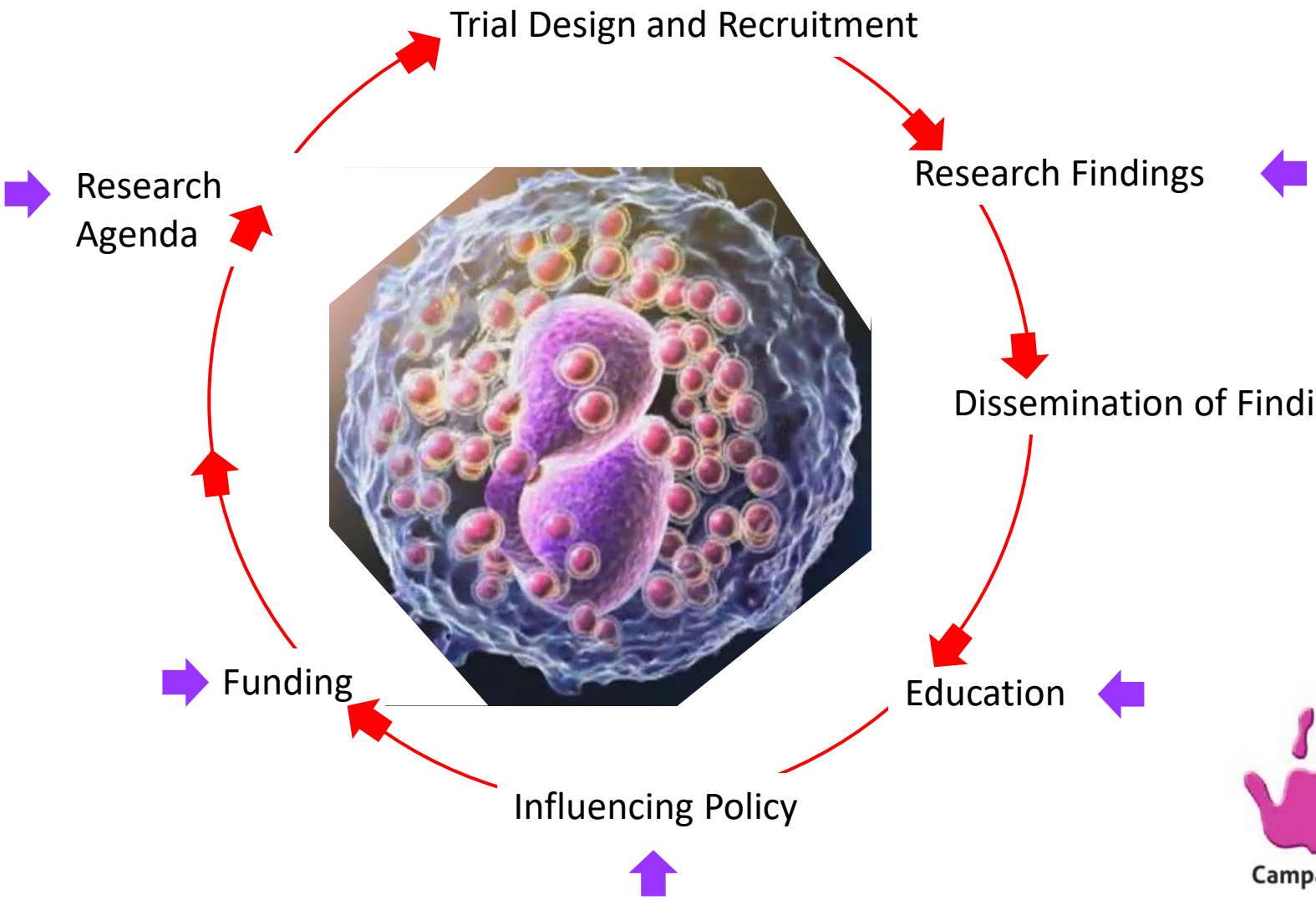
In January 2003, our daughter, Jori, was diagnosed with Eosinophilic Disease.
Within a year, CURED was founded. As its name suggests, Campaign Urging Research for Eosinophilic Disease is committed to finding a CURE. We began CURED at our kitchen table in a northwest suburb of Chicago. We now operate fundraisers across the country. To Date CURED has donated over $6,500,000 to medical research.

CURED is a not-for-profit foundation dedicated to those suffering from Eosinophilic Gastrointestinal Diseases (EGID), including eosinophilic esophagitis (EoE), eosinophilic gastritis (EoG), eosinophilic colitis (EoC), and other eosinophilic disorders. CURED is committed to raising substantial funding to aid in research, advocating on behalf of EGID patients and their families and working to educate and increase awareness about this complex group of diseases. It is our heartfelt belief that CURED can make a difference for the individuals and their families who are touched by these diseases.

- Patient Voice with Consortium of Eosinophilic Gastrointestinal Disease Researchers (CEGIR)
- Host Bi-Annual Meeting for medical professionals, patients, and industry
- Assist with recruitment for clinical trials
- Provide patient knowledge for pharma surveys
- Speak with FDA about the importance of drug approval

CURED
Campaign Urging Research for Eosinophilic Disease

CURED Foundation
Shaped Our Research at Multiple Entry Points



Campaign Urging Research for Eosinophilic Disease

Progression of Interactions with FDA and Other Stakeholders

CURED started introducing the challenges of eosinophilic disease patients' quality of life

17 Years ago

- CURED introduced the challenges of quality of life in patients with Eosinophilic Disease
- Removing 1-6 food elimination diets to removing all food and relying on elemental formula only. IMAGINE LIFE WITHOUT FOOD!

10 Years ago

- Pharmaceutical companies became interested in hearing about the patient voice, adult and pediatric patients.
- Employees became motivated by patients' personal stories and why it was important for their drug development.

6 Years ago

- CURED invited patients to share their emotional and medical journey for researchers, pharmaceutical companies, FDA, and other industry to hear their real-life experiences.
- CURED Patient Education Conferences featuring live patient experiences has been a major turning point to bringing the reality of how desperately patients need treatment.

Current

- Due to CURED's Involvement working one on one with patient families across the world, it is noted that CURED's outreach is making a tremendous difference filling clinical trials, disseminating surveys, and development of questionnaires to be presented to patients. It is crucial for Patient Advocacy Groups, like CURED to help move research forward.

CURED
Campaign Urging Research for Eosinophilic Disease

Endoscopic Reference Score (EREFS) and Dysphagia Symptom Questionnaire (DSQ)

The endoscopic reference score (EREFS) is used to determine severity of 5 endoscopic findings: edema, rings, exudates, furrows, and strictures. Little is known about the relationship between EREFSs and histologic markers of disease activity in children with eosinophilic esophagitis (EoE).

CURED was instrumental in recruiting patients for these clinical studies that helped identify these reference numbers.

Dysphagia Symptom Questionnaire (DSQ) is a 3-item patient-reported outcome measure that was successfully developed and tested. The DSQ had content validity and the score accurately measured dysphagia frequency and intensity.

CURED helped develop and disseminate the DSQ.
The more researchers, pharmaceutical companies, and FDA hear the patient voice, the more it gives them a clear understanding of the how greatly FDA-approved medications are needed.

Campaign Urging Research for Eosinophilic Disease

Hudgens S, Evans C, Phillips E, Hill M. Psychometric validation of the Dysphagia Symptom Questionnaire in patients with eosinophilic esophagitis treated with budesonide oral suspension. J Patient Rep Outcomes. 2017;1(1):3. doi: 10.1186/s41687-017-0006-5. Epub 2017 Sep 12. PMID: 29757322; PMCID: PMC5934937.

Progress Toward FDA Approval

Field Advances Across the Years

1980s
IL-4 discovered

1990s
IL-13 discovered

2000-2004
Allergens shown to induce EoE in mice (experimental EoE)

IL-13 shown to induce experimental EoE

Patient Advocacy Groups formed

CURED

2005-2009
Identification of EoE molecular signature

Blocking IL-13 shown to reduce experimental EoE

IL-13 shown to partially induce EoE molecular signature

IL-13 shown to be elevated in EoE

Discussions with Pharmaceutical Companies

Anti-IL-13 (QAX576) trial in humans initiated

2010-2014
First infusions with anti-IL-13 (QAX576)

Key clinical outcome metrics developed (DSQ, EREFS)

Formation of CEGIR

2015-2019
Positive trial results with anti-IL-13 (QAX576)

Positive phase II trial results for another anti-IL-13 (RPC4046) and Dupilumab (anti-IL-4Rα)

Additional clinical outcome metric developed (HSS)

Dupilumab phase III trial launched

2020-2022
Positive phase III trial results with Dupilumab

Phase III trial initiated for Cendakimab (anti-IL-13, formerly "RPC4046")

FDA approves Dupilumab (12+ years old)

CURED
Campaign Urging Research for Eosinophilic Disease

Eosinophilic Diseases
A set of diseases characterized by excess eosinophils (eosinophilia)

These rare diseases are diagnosed according to where the elevated levels of eosinophils are found:

Eosinophilic esophagitis
EOE
•Eosinophilic gastritis
EoG
•Eosinophilic enteritis
EoD
•Eosinophilic colitis
•EOC
•Hypereosinophilic Syndrome
•HES
•Eosinophilic Asthma

Symptoms

- **Pain**
- **Swelling**
- **Skin Rash**
- **Hives**
- **Reflux**
- **Choking**
- **Difficulty Swallowing**
- **Nausea**
- **Vomiting**
- **Loss of Appetite**
- **Stools Containing Blood and/or Mucus**
- **Abdominal Cramping**
- **Diarrhea**
- **Pseudopolyps**
- **Protein Loss**
- **Anemia**
- **Malabsorption**
- **Developmental Delay**
- **Bleeding**
- **Nutritional Deficiencies**

Current Treatment Limitations

Treatment Options:

- Complete healing of the esophagus, stomach, duodenum, colon
- Resolution of the functional impairment of the disease
- To improve quality of life
- Prevent disease recurrence after remission
- Limit treatment side effects

Treatment Limitations:

- Only one FDA-approved drug for EOE
- No approved drugs for lower EGID
- Patients must use off-label therapy
- Relapsing and refractory diseases
- Unknown side effects from long-term use of off-label therapies
- Patients must balance the burden of disease, cost, and therapy

Contributors to Success of Treatment Approval for HES and EoE

- Long-term commitment
- Patient partnership and support, such as key philanthropic financial support of research by the CURED Foundation
- Investment and expertise in basic and translational science
- Proof-of-concept (pre-industry)
- Clinical trial readiness
- Industry partnership
- Engagement of key stakeholders, especially NIH, FDA, and patients

Campaign Urging Research for Eosinophilic Disease

CURED and the patient community are grateful for our first FDA approved drug in May 2022.

CURED
Campaign Urging Research for Eosinophilic Disease

CURED continues to work with stakeholders and FDA to get more options approved for our community.

Patient Experience Data: Use in Regulatory Decision Making and Labeling

Sarrit Kovacs, Ph.D.

Clinical Reviewer, Division of Gastroenterology (DG)

Office of Immunology and Inflammation (OII), Office of New Drugs (OND)

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

14th Annual Patient-Reported Outcome Consortium Workshop

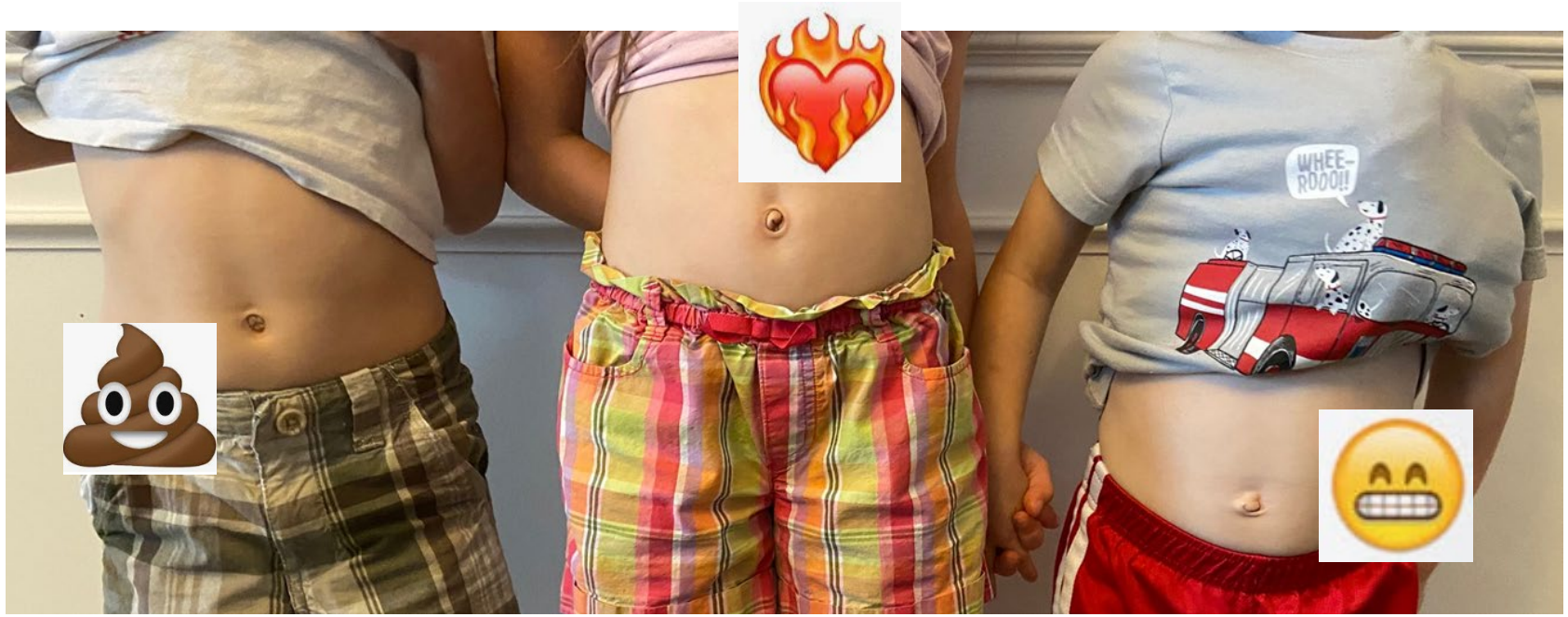
April 19, 2023

Disclosure Statement

- No conflicts of interest
- Nothing to disclose
- This talk reflects the views of the author and, unless otherwise noted, should not be construed to represent FDA's views or policies
- In this talk "drug" refers to both drugs and biologics

Thank you from FDA and the Division of Gastroenterology

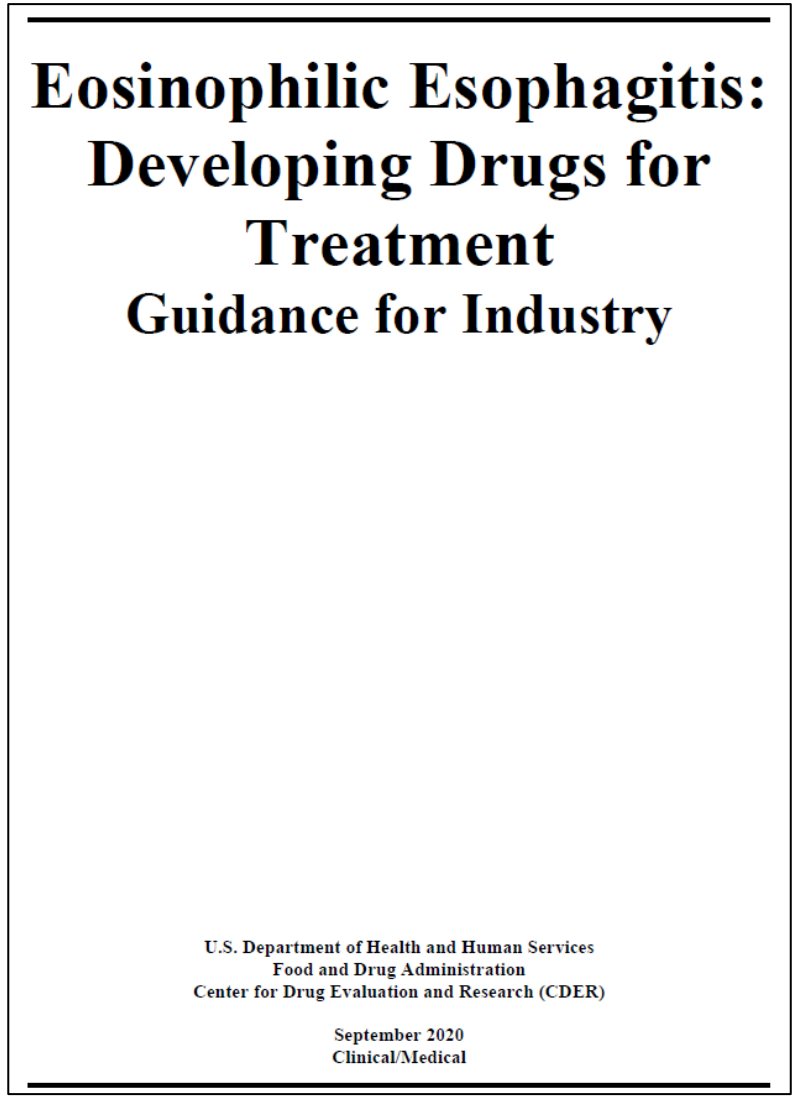
Why are PROs Commonly Used in GI?



- In many GI disorders, patients commonly experience symptoms that have substantial impact
- Outcomes such as irreversible morbidity or mortality occur infrequently and are not practical to assess

Additional Disclosure: Patient models for common GI symptoms were compensated with M&Ms for their participation and contribution.

Recent FDA Guidance from Gastroenterology

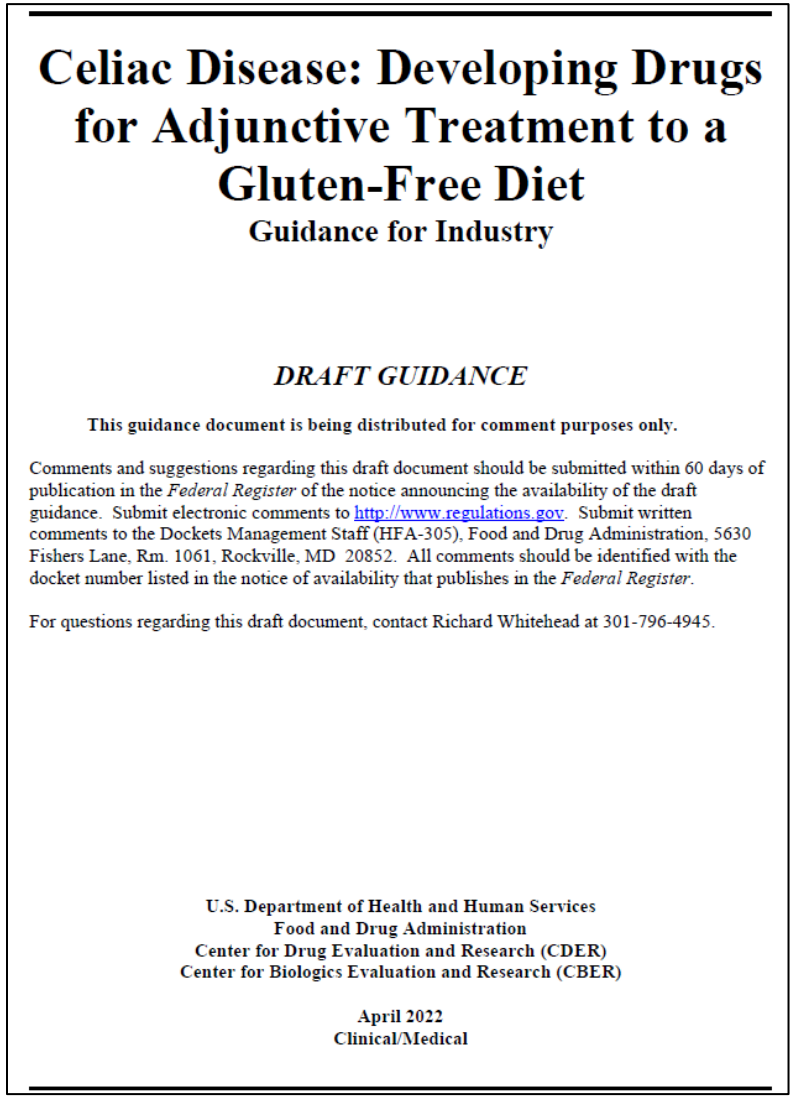


Eosinophilic Esophagitis: Developing Drugs for Treatment

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

September 2020
Clinical/Medical



Celiac Disease: Developing Drugs for Adjunctive Treatment to a Gluten-Free Diet

Guidance for Industry

DRAFT GUIDANCE

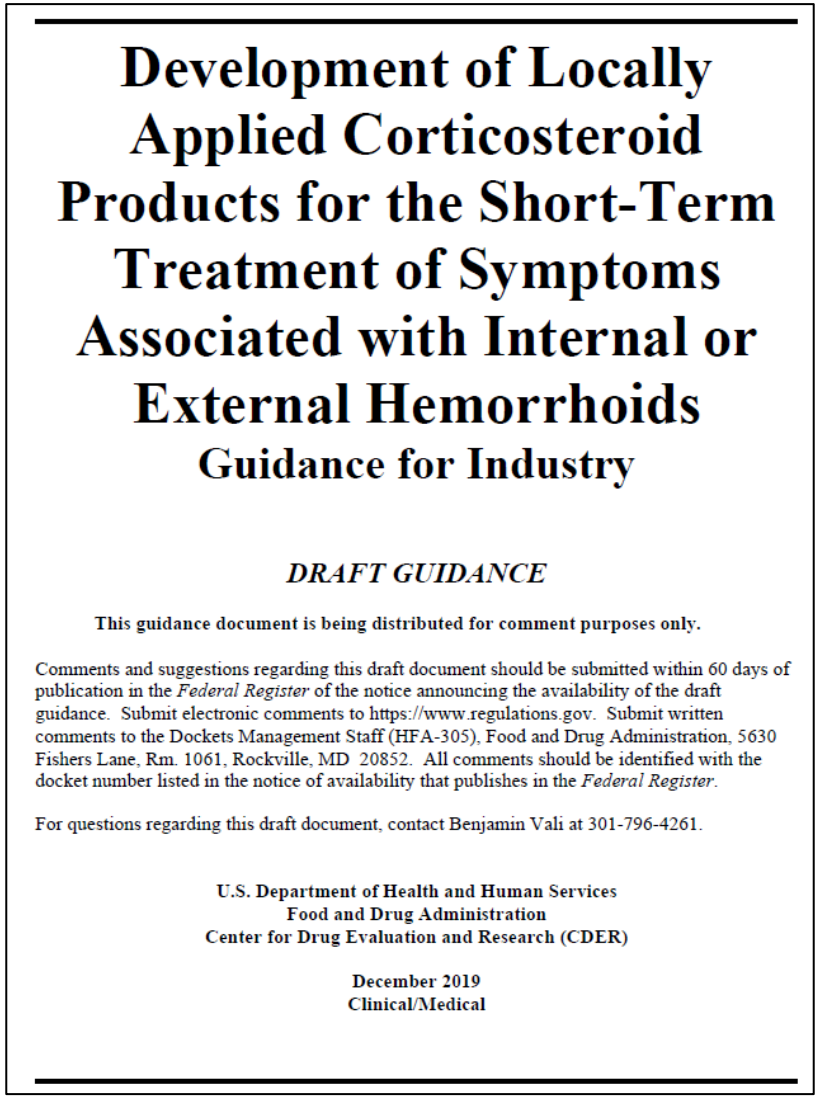
This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact Richard Whitehead at 301-796-4945.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

April 2022
Clinical/Medical



Development of Locally Applied Corticosteroid Products for the Short-Term Treatment of Symptoms Associated with Internal or External Hemorrhoids

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

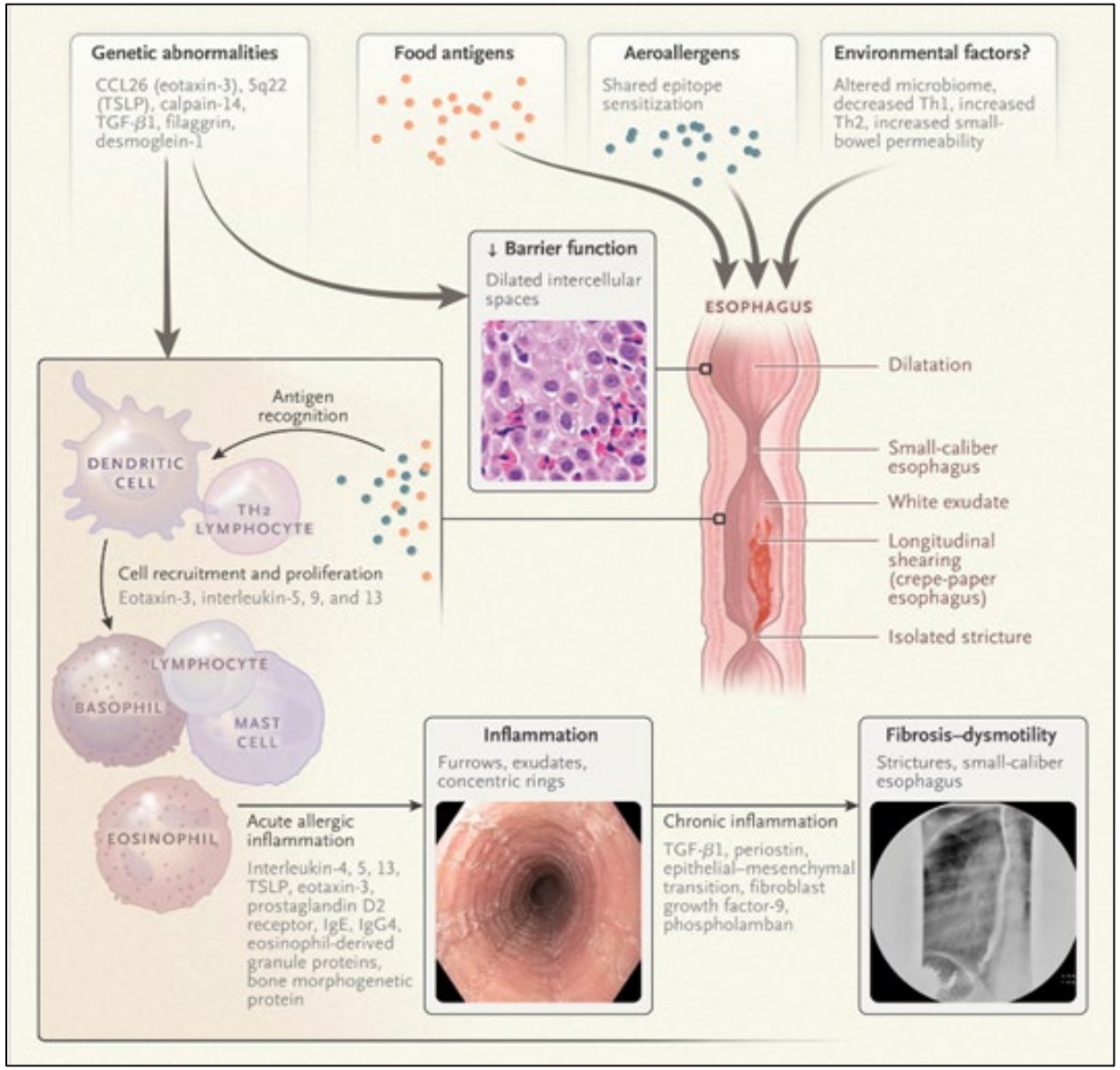
For questions regarding this draft document, contact Benjamin Vali at 301-796-4261.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

December 2019
Clinical/Medical

We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

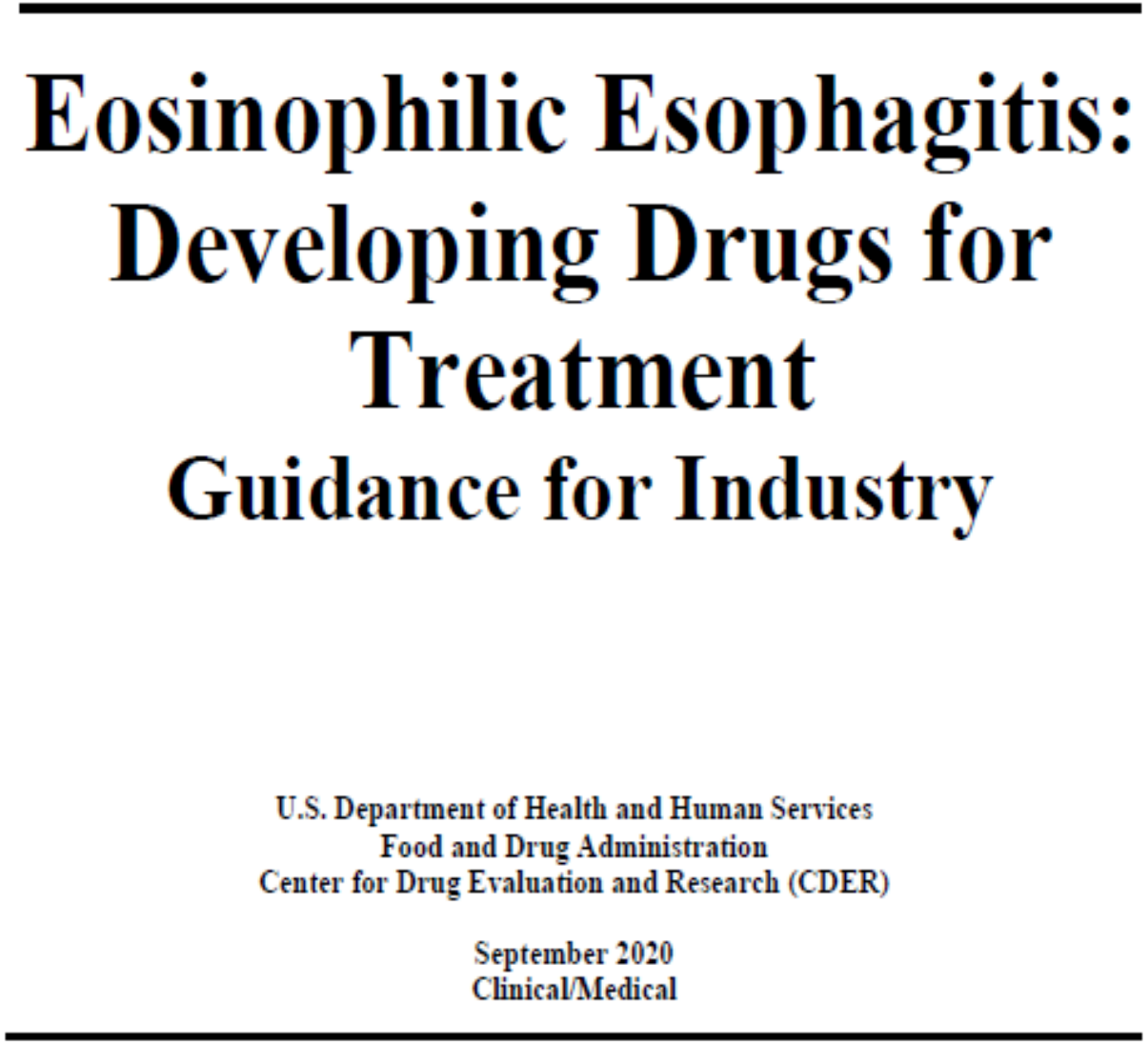
Background: Eosinophilic Esophagitis (EoE)



Furuta, G and Katzka, D . Eosinophilic Esophagitis. N Engl J Med 2015; 373:1640-1648, October 22, 2015. DOI: 10.1056/NEJMra1502863

- By current estimates, EoE affects somewhere between 1-2/2000 people
  - (prevalence of 0.5-1 cases per 1000 persons[1])
- ~166,000 – 332,000 children and adults in the US with EoE[2]

1- Dellon ES, Jensen ET, Martin CF, Shaheen NJ, Kappelman MD. Prevalence of eosinophilic esophagitis in the United States. Clin Gastroenterol Hepatol. 2014 Apr;12(4):589-96.e1. doi: 10.1016/j.cgh.2013.09.008. Epub 2013 Sep 11. PMID: 24035773; PMCID: PMC3952040.
2- United States Census Bureau, Population Clock. The US population was 332,825,548 on June 27, 2022.



Coprimary Endpoints

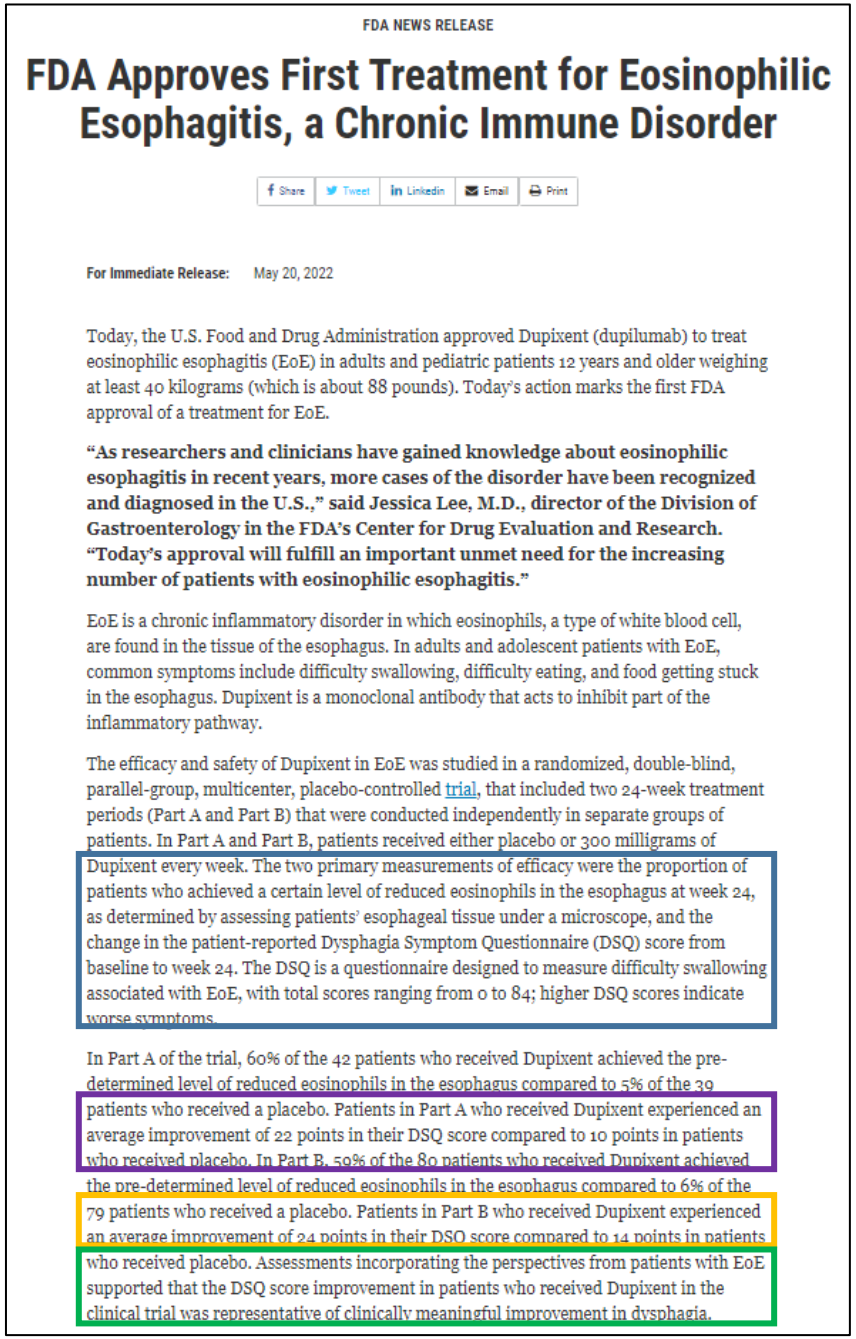
- Assess significant improvement from baseline in signs and symptoms, compared to placebo, using a well-defined and reliable clinical outcome assessment (COA)
  - Clinically meaningful effect that is considered a treatment benefit by patients
- Document a histologic response of peak eosinophil per HPF of ≤ 6 across all available esophageal levels

The two primary measurements of efficacy were the proportion of patients who achieved a certain level of reduced eosinophils in the esophagus at week 24, as determined by assessing patients' esophageal tissue under a microscope, and the change in the patient-reported Dysphagia Symptom Questionnaire (DSQ) score from baseline to week 24. The DSQ is a questionnaire designed to measure difficulty swallowing associated with EoE, with total scores ranging from 0 to 84; higher DSQ scores indicate worse symptoms.

Patients in Part A who received Dupixent experienced an average improvement of 22 points in their DSQ score compared to 10 points in patients who received placebo.

Patients in Part B who received Dupixent experienced an average improvement of 24 points in their DSQ score compared to 14 points in patients who received placebo.

Assessments incorporating the perspectives from patients with EoE supported that the DSQ score improvement in patients who received Dupixent in the clinical trial was representative of clinically meaningful improvement in dysphagia.



FDA NEWS RELEASE

FDA Approves First Treatment for Eosinophilic Esophagitis, a Chronic Immune Disorder

Share Tweet LinkedIn Email Print

For Immediate Release: May 20, 2022

Today, the U.S. Food and Drug Administration approved Dupixent (dupilumab) to treat eosinophilic esophagitis (EoE) in adults and pediatric patients 12 years and older weighing at least 40 kilograms (which is about 88 pounds). Today's action marks the first FDA approval of a treatment for EoE.

"As researchers and clinicians have gained knowledge about eosinophilic esophagitis in recent years, more cases of the disorder have been recognized and diagnosed in the U.S.," said Jessica Lee, M.D., director of the Division of Gastroenterology in the FDA's Center for Drug Evaluation and Research. "Today's approval will fulfill an important unmet need for the increasing number of patients with eosinophilic esophagitis."

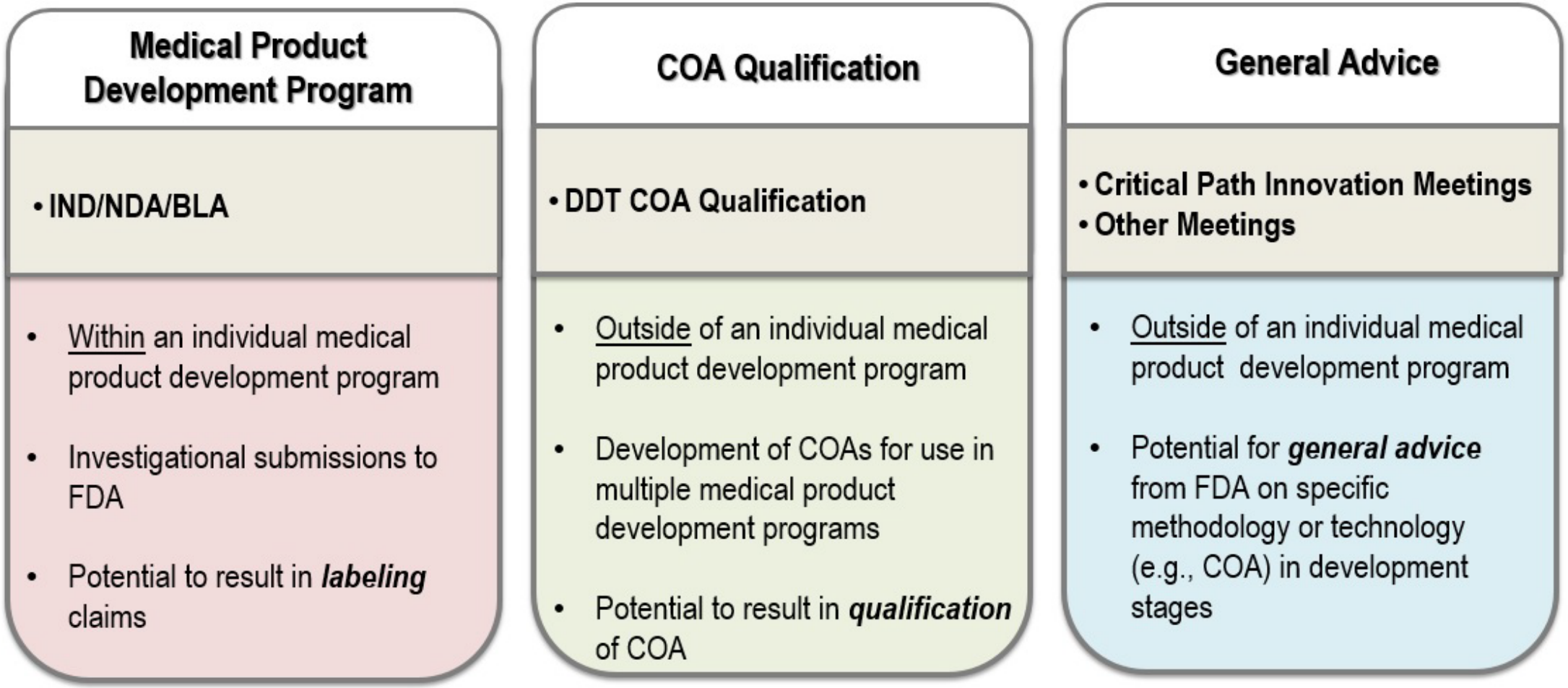
EoE is a chronic inflammatory disorder in which eosinophils, a type of white blood cell, are found in the tissue of the esophagus. In adults and adolescent patients with EoE, common symptoms include difficulty swallowing, difficulty eating, and food getting stuck in the esophagus. Dupixent is a monoclonal antibody that acts to inhibit part of the inflammatory pathway.

The efficacy and safety of Dupixent in EoE was studied in a randomized, double-blind, parallel-group, multicenter, placebo-controlled trial, that included two 24-week treatment periods (Part A and Part B) that were conducted independently in separate groups of patients. In Part A and Part B, patients received either placebo or 300 milligrams of Dupixent every week. The two primary measurements of efficacy were the proportion of patients who achieved a certain level of reduced eosinophils in the esophagus at week 24, as determined by assessing patients' esophageal tissue under a microscope, and the change in the patient-reported Dysphagia Symptom Questionnaire (DSQ) score from baseline to week 24. The DSQ is a questionnaire designed to measure difficulty swallowing associated with EoE, with total scores ranging from 0 to 84; higher DSQ scores indicate worse symptoms.

In Part A of the trial, 60% of the 42 patients who received Dupixent achieved the pre-determined level of reduced eosinophils in the esophagus compared to 5% of the 39 patients who received a placebo. Patients in Part A who received Dupixent experienced an average improvement of 22 points in their DSQ score compared to 10 points in patients who received placebo. In Part B, 59% of the 80 patients who received Dupixent achieved the pre-determined level of reduced eosinophils in the esophagus compared to 6% of the 79 patients who received a placebo. Patients in Part B who received Dupixent experienced an average improvement of 24 points in their DSQ score compared to 14 points in patients who received placebo. Assessments incorporating the perspectives from patients with EoE supported that the DSQ score improvement in patients who received Dupixent in the clinical trial was representative of clinically meaningful improvement in dysphagia.

FDA News Release May 20, 2022. Available: FDA Approves First Treatment for Eosinophilic Esophagitis, a Chronic Immune Disorder | FDA

Pathways for Partnership to Facilitate Drug Development



BLA = Biologics Licensing Application; **COA =** Clinical Outcome Assessment; **DDT =** Drug Development Tool;
IND = Investigational New Drug; **NDA =** New Drug Application

In Closing

- Capturing the patient voice and ensuring robust, meaningful, and representative input is vital in advancing patient-focused drug development
- Implementation of patient-focused drug development has had broad impacts on the evaluation of new drugs across the FDA


FDA
U.S. FOOD & DRUG
ADMINISTRATION

Patient Experience Data: Bringing the Patient Experience to FDA and Other Stakeholders

Marc Yale
Advocacy and Research Coordinator
International Pemphigus Pemphigoid Foundation (IPPF)

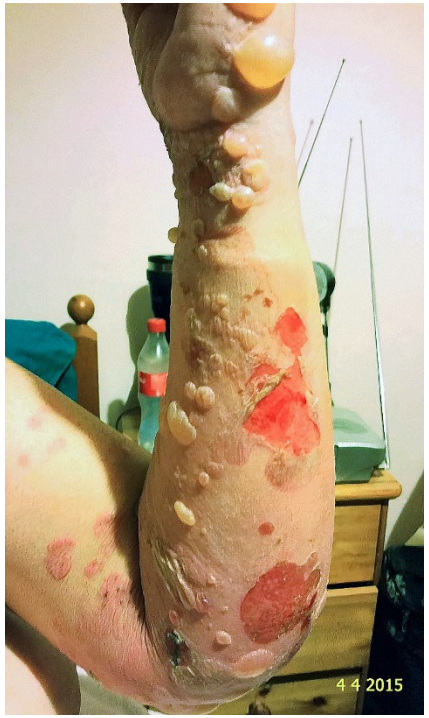
Autoimmune Bullous Disease (AIBD) Background

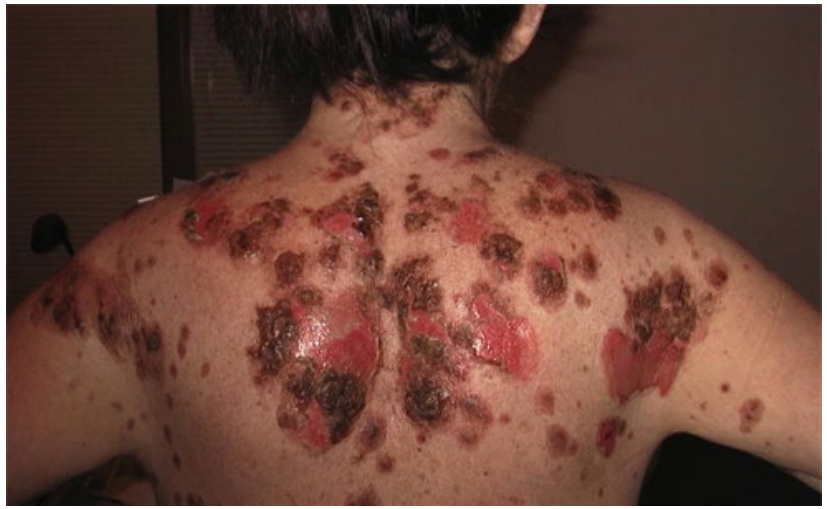
- **Pemphigus**
  - Intra-epidermal
    - Pemphigus vulgaris (PV)
    - Pemphigus foliaceus/superficial (PF)
    - Paraneoplastic pemphigus (PNP)
  - Antibodies directed against proteins of the desmosomes
  - Incidence: Overall standardized point prevalence of 5.2 cases per 100 000 adults (Wertenteil et al, JAMA Dermatol 2019)

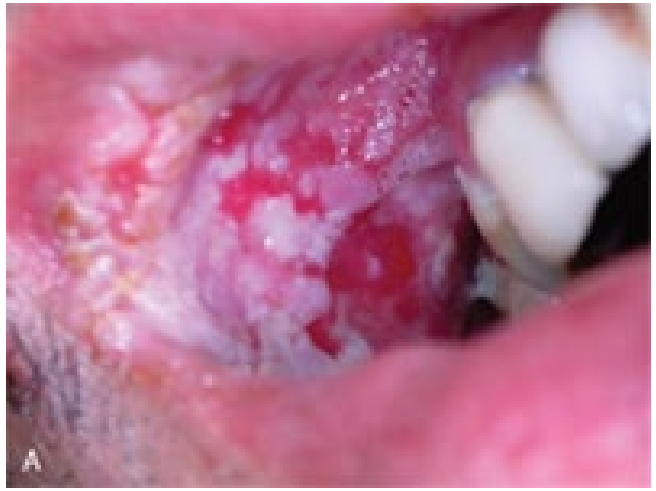
- **Pemphigoid**
  - Sub-epidermal
    - Bullous pemphigoid (BP) – the most common
    - Mucous membrane pemphigoid (MMP)
    - Pemphigoid gestationis (PG)
    - Epidermolysis bullosa acquisita (EBA)
    - Anti-p200 pemphigoid
    - Linear IgA bullous dermatosis (LABD)
  - Antibodies directed against adhesion proteins of the dermal/epidermal junction
  - Incidence: 12 pemphigoid patients/100,000 adults (Wertenteil et al, JAAD 2019)

Clinical Symptoms/Impact of Disease

- Pain from skin, oral, and genital erosions
- Trouble eating or swallowing
- Pruritus (particularly for bullous pemphigoid)
- Fear of relapse and having to take corticosteroids
- Stigmatization from visible blisters and scarring
- Anxiety/depression
- Weight loss/weight gain
- Insomnia
- Fatigue
- Corticosteroid side effects
- Scarring
- Bruising
- Infection
- Loss of work







https://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/dermatology/blistering-diseases/;
https://link.springer.com/chapter/10.1007/978-3-030-21855-3_6

2023 IPPF Externally Led-Patient-Focused Drug Development (EL-PFDD) Meeting

"Understanding the Unmet Needs of the Pemphigus and Pemphigoid Community" – January 25, 2023

Meeting Expectations:

- Understand patient perspectives
- Illustrate burden of the diseases
- Identify areas of unmet need
- Collect patient experience data
  - Live polling during meeting
  - Collect patient experience data pre/post EL-PFDD Meeting
- Utilize qualitative research methods
- Define meaningful benefit of therapeutic interventions
- Publish Voice of the Patient Report

Treatment Strategy Landscape

Suppress/eliminate disease-causing antibodies/B cells and suppress inflammation

- **Pemphigus**
  - FDA Approved: Corticosteroids (CS), Rituximab (RTX) – PV Only
  - Off Label:
    - Mycophenolate mofetil
    - Azathioprine
    - Methotrexate
    - Intravenous immunoglobulin (IVIg)

- **Pemphigoid**
  - FDA Approved: None
  - Off Label:
    - Topical steroids
    - Oral steroids (CS)
    - Doxycycline
    - Dapsone
    - Methotrexate
    - Mycophenolate mofetil
    - Azathioprine
    - Rituximab (RTX)
    - IVIg
    - Omalizumab/Dupilumab

Current Treatment Limitations

Treatment Goals:

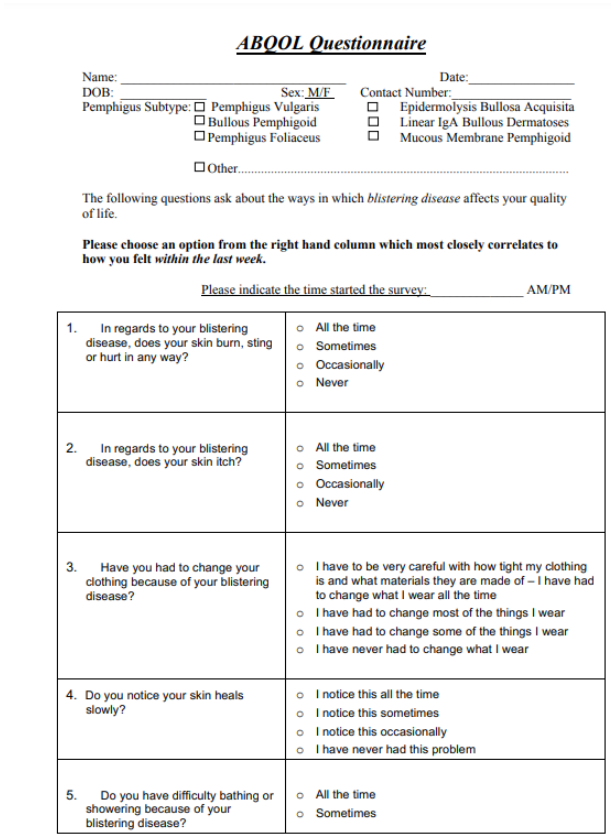
- Complete healing of blisters
- Resolution of the functional impairment associated with disease
- Improve quality of life
- Prevent disease recurrence
- Limit treatment side effects

Treatment Limitations:

- Few FDA approved drugs leaving patients faced with off-label therapies
- Relapsing and refractory diseases
- RTX and CS may include transient therapeutic effect, necessitating repeated infusions
- Most drugs for pemphigus and pemphigoid take several months to have therapeutic effect
- Chronic immune suppression leads to serious infections and impaired response to vaccines
- **Patients must balance the burden of disease with burden of therapy**

Validated Disease-Specific Instruments

- **Validated disease activity scales developed prior to PFDD era**
  - Pemphigus Disease Area Index (PDAI)
  - Autoimmune Bullous Skin Disorder Intensity Score (ABSIS)
  - Pemphigus Vulgaris Activity Score (PVAS)
  - Bullous Pemphigoid Disease Area Index (BPDAI)
  - Autoimmune Bullous Disease Quality of Life (ABQOL)
  - Treatment of Autoimmune Bullous Disease Quality of Life (TABQOL)



ABQOL Questionnaire

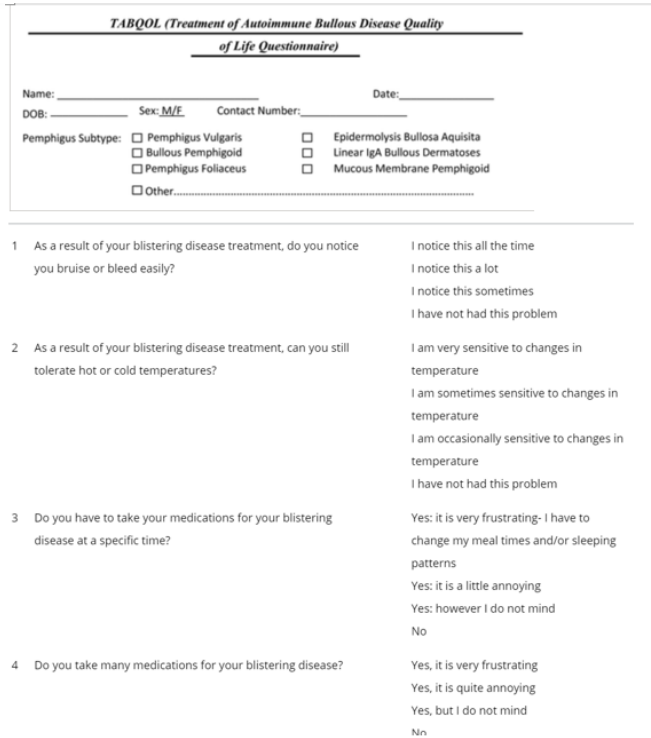
Name: _____ Date: _____
DOB: _____ Sex: M/F Contact Number: _____
Pemphigus Subtype: ☐ Pemphigus Vulgaris ☐ Epidermolysis Bullosa Acquisita
☐ Bullous Pemphigoid ☐ Linear IgA Bullous Dermatoses
☐ Pemphigus Foliaceus ☐ Mucous Membrane Pemphigoid
☐ Other.....

The following questions ask about the ways in which *blistering disease* affects your quality of life.

Please choose an option from the right hand column which most closely correlates to how you felt *within the last week*.

Please indicate the time started the survey: _____ AM/PM

1. In regards to your blistering disease, does your skin burn, sting or hurt in any way?	○ All the time ○ Sometimes ○ Occasionally ○ Never
2. In regards to your blistering disease, does your skin itch?	○ All the time ○ Sometimes ○ Occasionally ○ Never
3. Have you had to change your clothing because of your blistering disease?	○ I have to be very careful with how tight my clothing is and what materials they are made of – I have had to change what I wear all the time ○ I have had to change most of the things I wear ○ I have had to change some of the things I wear ○ I have never had to change what I wear
4. Do you notice your skin heals slowly?	○ I notice this all the time ○ I notice this sometimes ○ I notice this occasionally ○ I have never had this problem
5. Do you have difficulty bathing or showering because of your blistering disease?	○ All the time ○ Sometimes



TABQOL (Treatment of Autoimmune Bullous Disease Quality of Life Questionnaire)

Name: _____ Date: _____
DOB: _____ Sex: M/F Contact Number: _____
Pemphigus Subtype: ☐ Pemphigus Vulgaris ☐ Epidermolysis Bullosa Aquisita
☐ Bullous Pemphigoid ☐ Linear IgA Bullous Dermatoses
☐ Pemphigus Foliaceus ☐ Mucous Membrane Pemphigoid
☐ Other.....

1	As a result of your blistering disease treatment, do you notice you bruise or bleed easily?	I notice this all the time I notice this a lot I notice this sometimes I have not had this problem
2	As a result of your blistering disease treatment, can you still tolerate hot or cold temperatures?	I am very sensitive to changes in temperature I am sometimes sensitive to changes in temperature I am occasionally sensitive to changes in temperature I have not had this problem
3	Do you have to take your medications for your blistering disease at a specific time?	Yes: it is very frustrating- I have to change my meal times and/or sleeping patterns Yes: it is a little annoying Yes: however I do not mind No
4	Do you take many medications for your blistering disease?	Yes, it is very frustrating Yes, it is quite annoying Yes, but I do not mind No

Determining Endpoints

Reliability and validity of different disease activity instruments

- EL-PFDD data illustrates patients value improvement in disease activity
- Use similar endpoints that have previously led to drug approvals

Use of Investigator's Global Assessment (IGA) scale

- IGAs have not been co-developed by pemphigus and pemphigoid patients
- Scales should separate disease activity from damage
- Endpoints could instead be based on a percent reduction in disease specific activity scores

Endpoints for clinical trials should be comparable to those used for other similar diseases

Clinical Trial Endpoints and Meaningful Benefit

- Published 2008, Consensus statement on definitions of disease, end points, and therapeutic response for pemphigus - https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2829665/
- Published 2012, Definitions and outcome measures for bullous pemphigoid: recommendations by an international panel of experts - https://pubmed.ncbi.nlm.nih.gov/22056920/
  - Intended to assess standard of care therapies
  - Published before clinical trials were in development in the U.S.
  - Endpoints include complete or partial remission on minimal steroid doses or off steroids
  - Patients remain on the investigational therapy while being evaluated
- Minimal steroid doses for endpoints should also be considered carefully
- **Defining meaningful improvement is critical**
  - Data indicates that patients' quality of life can be restored despite not achieving complete remission of disease activity
  - Requiring complete disease clearance for clinical trials is not tied to meaningful responses for patients
  - Use of non-patient validated scales will ultimately impede drug development

The Voice of the Patient

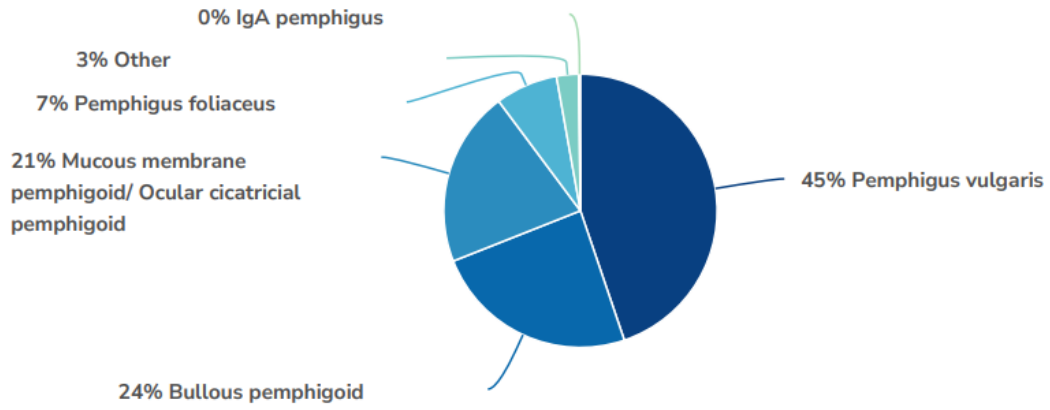
Collected Patient Experience Data Pre/Post EL-PFDD Meeting

Value	Percent	Responses
Pemphigus vulgaris	44.8%	224
Bullous pemphigoid	24.2%	121
Mucous membrane pemphigoid/ Ocular cicatricial pemphigoid	20.8%	104
Pemphigus foliaceus	7.4%	37
Other	2.6%	13
IgA pemphigus	0.2%	1

Totals: 500

Statistics	
Total Responses	500

1. Please indicate which disease you have.



Symptoms Having Most Significant Impact on QoL

Of all the symptoms that you experience because of your condition, please select the top 3 symptoms that have the most significant impact on your life? (Pick only 3)

Pain	50.5%	236
Trouble eating or swallowing	38.5%	180
Fatigue	34.5%	161
Itching	31.0%	145
Anxiety	24.0%	112
Wound care	22.5%	105
Bleeding from lesions	18.8%	88
Depression	11.6%	54
Infection due to immunosuppression	10.1%	47
Sleep disorder	9.6%	45
Impaired vision	7.7%	36

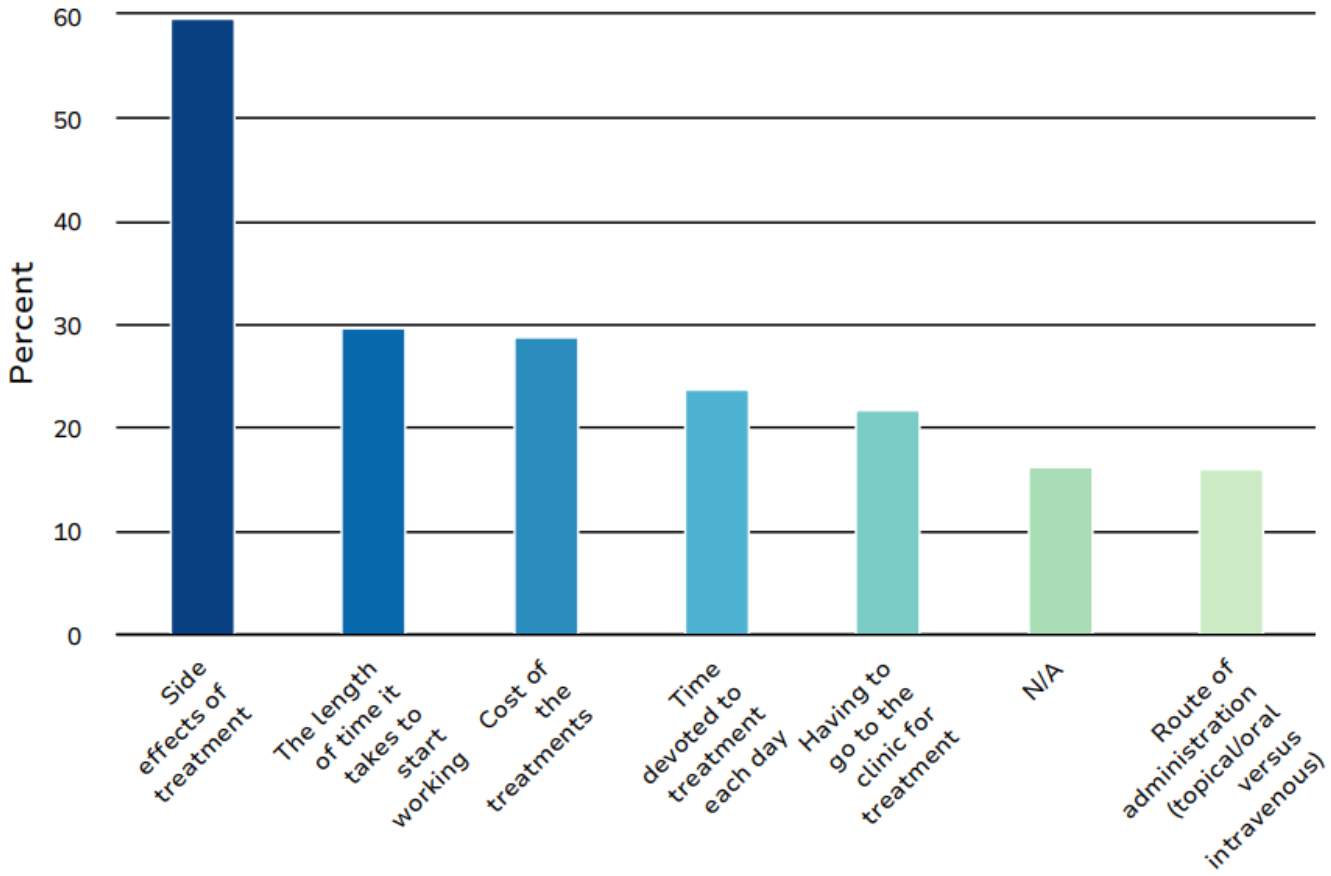
Disease Impact on Daily Activities

Which specific daily activities that are important to you are you unable to perform at all or as fully as you would like because of your condition? (Check all that apply)

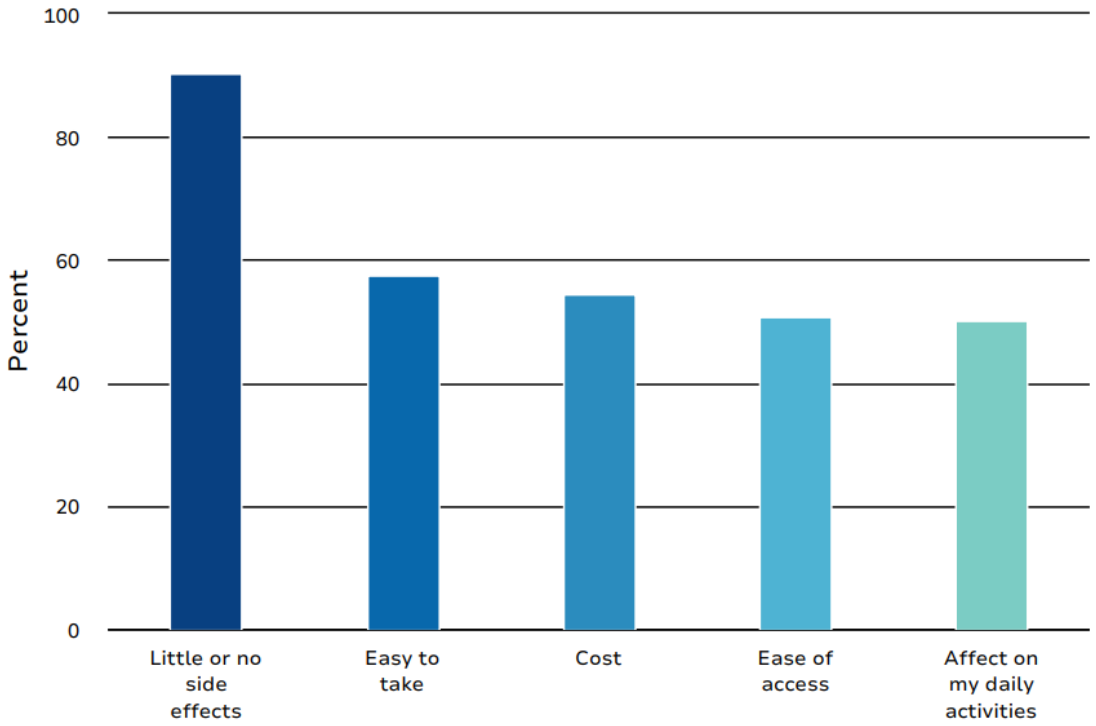
Value	Percent	Responses
Eating	40.2%	188
None, I am able to perform all my daily activities	29.5%	138
Study/concentrate	25.0%	117
Personal Hygiene	24.6%	115
Chores around the house	22.0%	103
Walking	19.0%	89
Mobility issues	17.3%	81
Talking	15.2%	71
Complex decision-making	14.5%	68
Impaired vision	12.2%	57

Downside of Current Treatments Effect on QoL

Value	Percent	Responses
Side effects of treatment	59.8%	269
The length of time it takes to start working	29.8%	134
Cost of the treatments	28.9%	130
Time devoted to treatment each day	23.8%	107
Having to go to the clinic for treatment	21.8%	98
N/A	16.4%	74
Route of administration (topical/oral versus intravenous)	16.0%	72



Ideal Treatments for Patient's Condition



Value	Percent	Responses
Little or no side effects	90.6%	406
Easy to take	57.8%	259
Cost	54.7%	245
Ease of access	50.9%	228
Affect on my daily activities	50.4%	226

Statistics

Total Responses	448

Ongoing Data Collection

IPPF Natural History Registry Study

- Launched in March 2017
- Collects, stores, and retrieves patient data for analysis in research studies
- Sponsored by NORD and FDA

Collects data on the following topics:

- Socio-demographics
- Medical and diagnostics
- Treatment and disease progression
- Management of care
- Quality of life

Value of Patient Advocacy Groups

Patient Experience Data is much more than just the data!

"Rare disease patients already have a lot to face just understanding where they are. Having to drag every single practitioner along that journey like a sherpa, losing time with family and work, failing treatment after treatment and waiting endlessly for approvals that come to us so late should be a thing of our past."

- **Patient Advocacy Groups provide:**
  - Direct link to patients, caregivers, and families
  - Trust – Have credibility
  - Unique perspective and research capabilities
    - Assist with academic studies
    - Clinical trial education and enrollment
    - Facilitate focus groups
    - Conduct natural history studies
      - Help develop clinical endpoints that have meaningful benefit

Key Take Aways

- Severe life-threatening diseases
- Cause significant burden
- Access to therapy remains an issue
- Few clinically approved drugs
- Most drugs prescribed off-label
- Balance of disease/therapy burden
- Control disease without serious side effects
- Use endpoints that reflect issues most important to patients
- Physical/psychological impacts
- Minimal therapy primary and complete remission secondary
- New drugs provide meaningful benefit
- Disease activity measures too stringent
- QoL restored despite not achieving “clear” or “almost clear”
- Collaboration is key

Panel Discussion and Q&A

Moderator

- *Sonya Eremenco, MA* – Executive Director, Patient-Reported Outcome Consortium, Critical Path Institute

Presenters and Panelists

- *Robyn Bent, RN, MS* – Director, Patient-Focused Drug Development Program, Center for Drug Evaluation and Research, U.S. Food and Drug Administration
- *Michelle Campbell, PhD* – Associate Director for Stakeholder Engagement and Clinical Outcomes, Office of Neuroscience, Office of New Drugs, Center for Drug Evaluation and Research, U.S. Food and Drug Administration
- *Ellyn Kodroff, BS* – President and Founder, CURED (Campaign Urging Research for Eosinophilic Diseases)
- *Sarrit Kovacs, PhD* – Clinical Reviewer, Division of Gastroenterology (DG), Office of Immunology and Inflammation (OII), Office of New Drugs (OND), Center for Drug Evaluation and Research (CDER), U.S. Food and Drug Administration (FDA)
- *Marc Yale* – Advocacy and Research Coordinator, International Pemphigus Pemphigoid Foundation (IPPF)

The Conversation Continues…

- ISPOR 2023, Boston, MA
  - Podium Presentation: Current Practices and Challenges When Submitting Patient Experience Data for US Regulatory Decision Making: An Industry Survey
  - Tuesday, May 9, 2023 – 4:45pm to 5:00pm

- DIA Global Annual Meeting, Boston, MA
  - Session: Patient Experience Data in the Label: Closing the Loop
  - Tuesday, June 27, 2023 – 10:30am to 11:30am

Thank you!