A Regulatory Perspective on Novel Efficacy Endpoints

Melissa Reyes, MD, MPH, DTMH
Division of Dermatology and Dental Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

I do not have any disclosures.

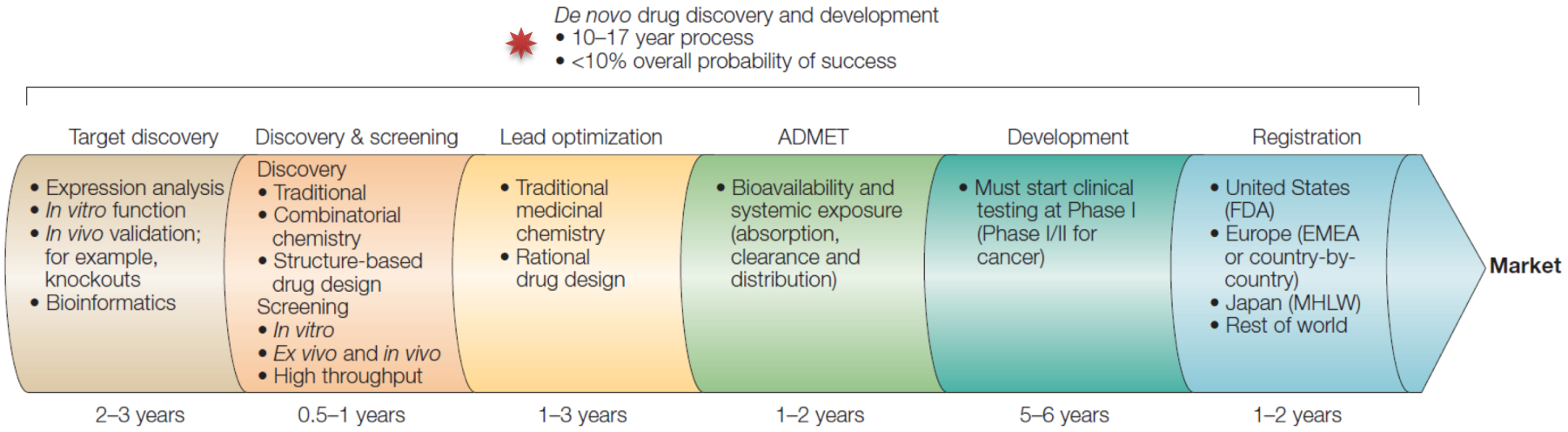
The opinions expressed are those of the presenter and do not reflect an official opinion of the FDA.

FDA CDER Mission

- PROMOTE PUBLIC HEALTH
  - by helping to ensure the availability of safe and effective drugs
- PROTECT PUBLIC HEALTH
  - by promoting the safe use of marketed drugs
  - by helping to ensure the quality and integrity of marketed drug products

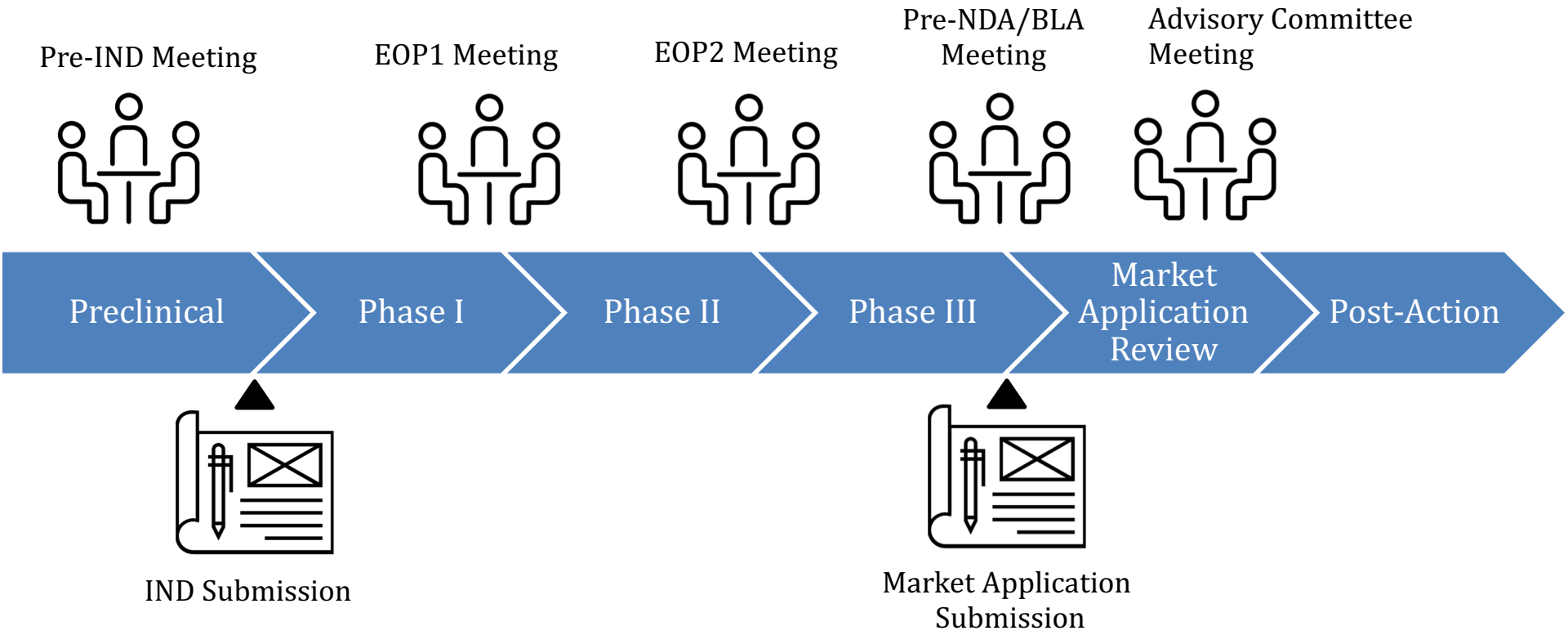

FDA

De novo Drug Discovery



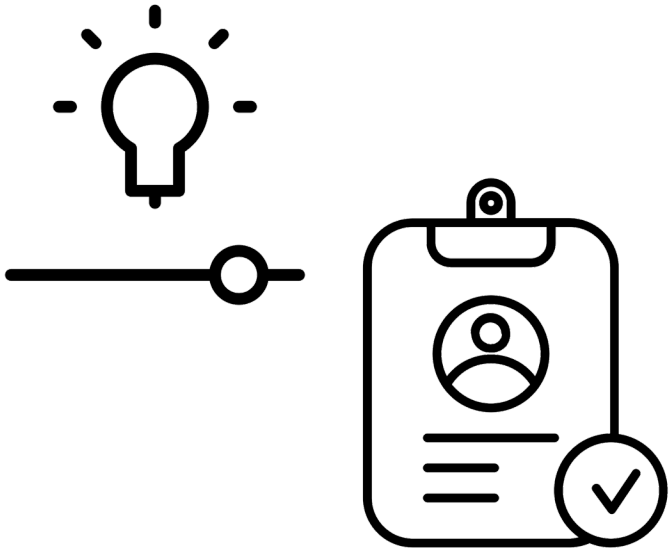
Ashburn and Thor Nature Reviews Drug Discovery, 2004

Ongoing FDA Support



Outline

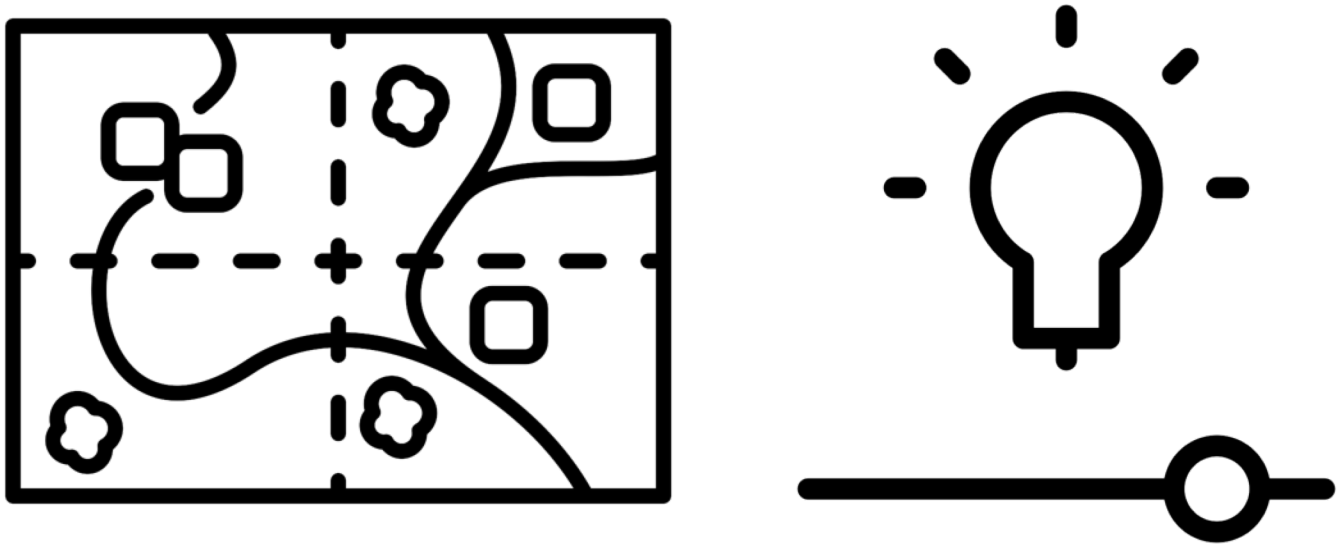
- Demonstrating efficacy in novel indications
- Addressing Patient Reported Outcomes
- Addressing Clinician Reported Outcomes



4 Key Points

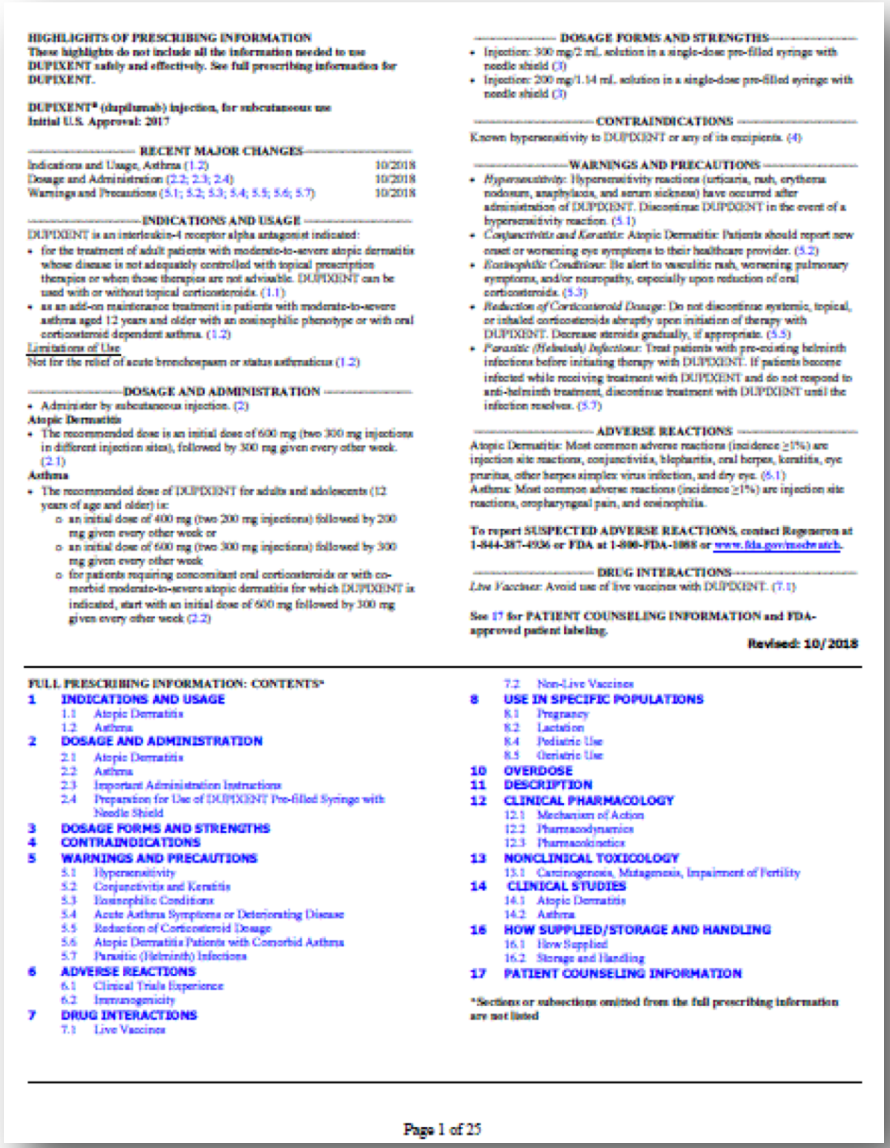
- Consult the published FDA Guidances
- Science – basic, clinical and regulatory - is continuously evolving
- Previous approvals can serve as a guiding post
- FDA is available to provide additional guidance through appropriate pathways

Demonstrating Efficacy Roadmap



Novel Efficacy Endpoints for Novel Indications

Prescribing Information



HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use DUPIXENT safely and effectively. See full prescribing information for DUPIXENT.

DUPIXENT® (dupilumab) injection, for subcutaneous use
Initial U.S. Approval: 2017

RECENT MAJOR CHANGES

Indications and Usage, Asthma (1.2)	10/2018
Dosage and Administration (2.2; 2.3; 2.4)	10/2018
Warnings and Precautions (5.1; 5.2; 5.3; 5.4; 5.5; 5.6; 5.7)	10/2018

INDICATIONS AND USAGE

DUPIXENT is an interleukin-4 receptor alpha antagonist indicated:

- for the treatment of adult patients with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. DUPIXENT can be used with or without topical corticosteroids. (1.1)
- as an add-on maintenance treatment in patients with moderate-to-severe asthma aged 12 years and older with an eosinophilic phenotype or with oral corticosteroid dependent asthma. (1.2)

Limitations of Use
Not for the relief of acute bronchospasm or status asthmaticus (1.2)

DOSAGE AND ADMINISTRATION

- Administer by subcutaneous injection. (2)

Atopic Dermatitis

- The recommended dose is an initial dose of 600 mg (two 300 mg injections in different injection sites), followed by 300 mg given every other week. (2.1)

Asthma

- The recommended dose of DUPIXENT for adults and adolescents (12 years of age and older) is:
  - an initial dose of 400 mg (two 200 mg injections) followed by 200 mg given every other week or
  - an initial dose of 600 mg (two 300 mg injections) followed by 300 mg given every other week
  - for patients requiring concomitant oral corticosteroids or with co-morbid moderate-to-severe atopic dermatitis for which DUPIXENT is indicated, start with an initial dose of 600 mg followed by 300 mg given every other week (2.2)

DOSAGE FORMS AND STRENGTHS

- Injection: 300 mg/2 mL solution in a single-dose pre-filled syringe with needle shield (3)
- Injection: 200 mg/1.14 mL solution in a single-dose pre-filled syringe with needle shield (3)

CONTRAINDICATIONS

Known hypersensitivity to DUPIXENT or any of its excipients. (4)

WARNINGS AND PRECAUTIONS

- *Hypersensitivity:* Hypersensitivity reactions (urticaria, rash, erythema nodosum, anaphylaxis, and serum sickness) have occurred after administration of DUPIXENT. Discontinue DUPIXENT in the event of a hypersensitivity reaction. (5.1)
- *Conjunctivitis and Keratitis:* Atopic Dermatitis: Patients should report new onset or worsening eye symptoms to their healthcare provider. (5.2)
- *Eosinophilic Conditions:* Be alert to vasculitic rash, worsening pulmonary symptoms, and/or neuropathy, especially upon reduction of oral corticosteroids. (5.3)
- *Reduction of Corticosteroid Dosage:* Do not discontinue systemic, topical, or inhaled corticosteroids abruptly upon initiation of therapy with DUPIXENT. Decrease steroids gradually, if appropriate. (5.5)
- *Parasitic (Helminth) Infections:* Treat patients with pre-existing helminth infections before initiating therapy with DUPIXENT. If patients become infected while receiving treatment with DUPIXENT and do not respond to anti-helminth treatment, discontinue treatment with DUPIXENT until the infection resolves. (5.7)

ADVERSE REACTIONS

Atopic Dermatitis: Most common adverse reactions (incidence ≥1%) are injection site reactions, conjunctivitis, blepharitis, oral herpes, keratitis, eye pruritus, other herpes simplex virus infection, and dry eye. (6.1)
Asthma: Most common adverse reactions (incidence ≥1%) are injection site reactions, oropharyngeal pain, and eosinophilia.

To report SUSPECTED ADVERSE REACTIONS, contact Regeneron at 1-844-387-4936 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Live Vaccines: Avoid use of live vaccines with DUPIXENT. (7.1)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

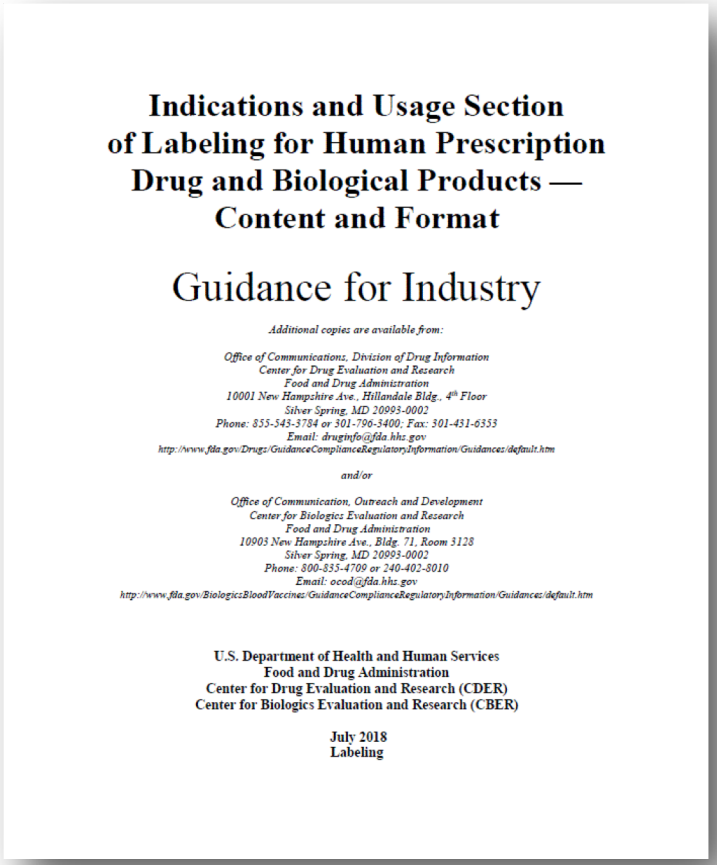
Revised: 10/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
1.1 Atopic Dermatitis
1.2 Asthma
2 DOSAGE AND ADMINISTRATION
2.1 Atopic Dermatitis
2.2 Asthma
2.3 Important Administration Instructions
2.4 Preparation for Use of DUPIXENT Pre-filled Syringe with Needle Shield
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Hypersensitivity
5.2 Conjunctivitis and Keratitis
5.3 Eosinophilic Conditions
5.4 Acute Asthma Symptoms or Deteriorating Disease
5.5 Reduction of Corticosteroid Dosage
5.6 Atopic Dermatitis Patients with Comorbid Asthma
5.7 Parasitic (Helminth) Infections
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
6.2 Immunogenicity
7 DRUG INTERACTIONS
7.1 Live Vaccines
7.2 Non-Live Vaccines
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation
8.4 Pediatric Use
8.5 Geriatric Use
10 OVERDOSE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
14 CLINICAL STUDIES
14.1 Atopic Dermatitis
14.2 Asthma
16 HOW SUPPLIED/STORAGE AND HANDLING
16.1 How Supplied
16.2 Storage and Handling
17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed

- "the label"
- In every prescription drug you pick up at the pharmacy



Indications and Usage Section of Labeling for Human Prescription Drug and Biological Products — Content and Format

Guidance for Industry

Additional copies are available from:

Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353
Email: druginfo@fda.hhs.gov
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

and/or

Office of Communication, Outreach and Development
Center for Biologics Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 71, Room 3128
Silver Spring, MD 20993-0002
Phone: 800-835-4709 or 240-402-8010
Email: ocod@fda.hhs.gov
http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

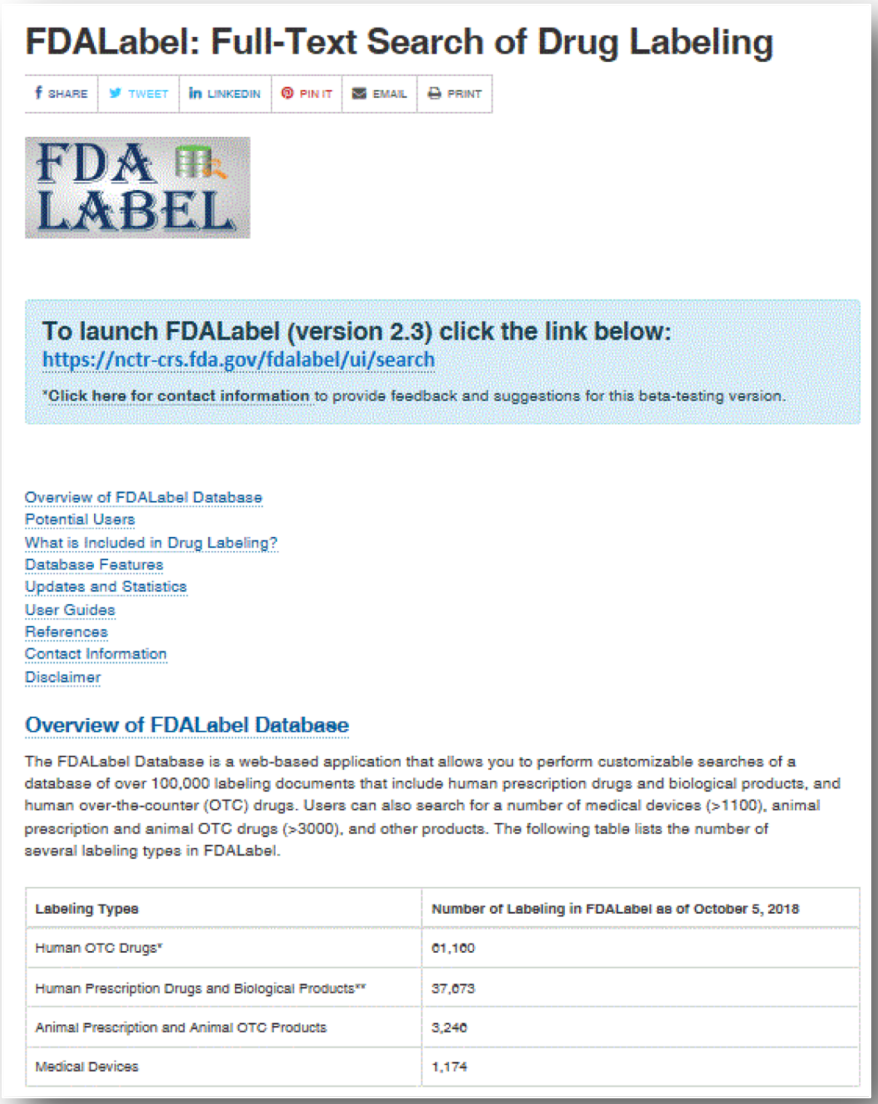
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

July 2018
Labeling

Drug Indication

- Section 1: Indications and Usage
  - The disease, condition, or manifestation of the disease or condition (e.g., symptom(s)) being treated, prevented, mitigated, cured, or diagnosed
  - “all indications listed…must be supported by substantial evidence of effectiveness based on adequate and well-controlled studies”

https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM612697.pdf



FDALabel: Full-Text Search of Drug Labeling

SHARE TWEET LINKEDIN PIN IT EMAIL PRINT

FDA LABEL

To launch FDALabel (version 2.3) click the link below:
https://nctr-crs.fda.gov/fdalabel/ui/search

*Click here for contact information to provide feedback and suggestions for this beta-testing version.

Overview of FDALabel Database
Potential Users
What is Included in Drug Labeling?
Database Features
Updates and Statistics
User Guides
References
Contact Information
Disclaimer

Overview of FDALabel Database

The FDALabel Database is a web-based application that allows you to perform customizable searches of a database of over 100,000 labeling documents that include human prescription drugs and biological products, and human over-the-counter (OTC) drugs. Users can also search for a number of medical devices (>1100), animal prescription and animal OTC drugs (>3000), and other products. The following table lists the number of several labeling types in FDALabel.

Labeling Types	Number of Labeling in FDALabel as of October 5, 2018
Human OTC Drugs*	61,160
Human Prescription Drugs and Biological Products**	37,673
Animal Prescription and Animal OTC Products	3,246
Medical Devices	1,174

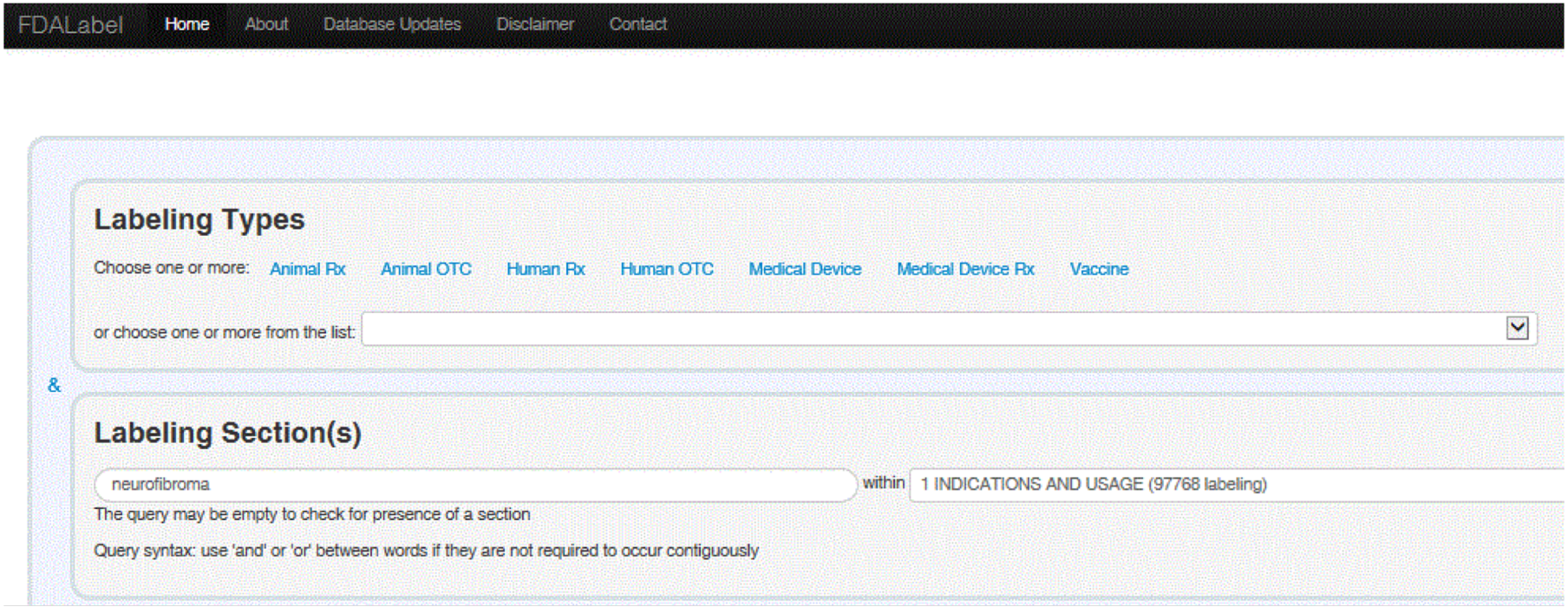
FDALabel

- Searchable database of FDA-approved labeling documents
  - New Drug Applications (NDAs)
  - Biologic Licensing Applications (BLAs)
  - Over-the-counter (OTC)

  - Some: devices, veterinary drugs

https://www.fda.gov/ScienceResearch/BioinformaticsTools/ucm289739.htm

FDALabel



Novel indication: treatment of (cutaneous) neurofibromas

FDALabel

Search: NDA, Indication - pruritus

35 labeling results

Basic View | Expanded View

Download Full

Links	Labeling Type	Dosage Form(s)	Route(s) of Administration	Trade Name	▲Generic/Proper Name(s)
SPL Document DailyMed (pdf) Drugs@FDA 019826; Orange Book 019826;	HUMAN PRESCRIPTION DRUG LABEL	CAPSULE	ORAL	SEMPREX D	ACRIVASTINE AND PSEUDOEPHEDRINE HYDROCHLORIDE
SPL Document DailyMed (pdf) Drugs@FDA 204200; Orange Book 204200;	HUMAN PRESCRIPTION DRUG LABEL	INJECTION	INTRAMUSCULAR; SUBCUTANEOUS	ADRENALIN (EPINEPHRINE)	ADRENALIN (EPINEPHRINE)
SPL Document DailyMed (pdf)	HUMAN PRESCRIPTION DRUG LABEL	INJECTION	INTRAMUSCULAR; SUBCUTANEOUS	ADRENALIN(R)	ADRENALIN(R)

Search: NDA, Indication - pruritus

INDICATIONS AND USAGE

Zonalon® Cream is indicated for the short-term (up to 8 days) management of moderate pruritus in adult patients with atopic dermatitis or lichen simplex chronicus.

CLINICAL EFFICACY ENDPOINTS

General Attributes of Clinical Endpoints

- Clinical endpoints should:
  - be clinically meaningful
  - reflect how a patient feels, functions, or survives
  - be reliably measured
- Showing a treatment effect is dependent on:
  - the disease and its manifestations
  - the course of disease over time
  - what is being assessed and when assessed
  - confounders which introduce variability (genetic, environmental, meds)
  - the effect size of the drug
    - large effect size can mitigate some of the uncertainty associated with an endpoint and how it is measured
  - For dermatologic conditions, how a patient looks (cosmesis) may be a relevant clinical effect.

Clinical Trial Efficacy Endpoints

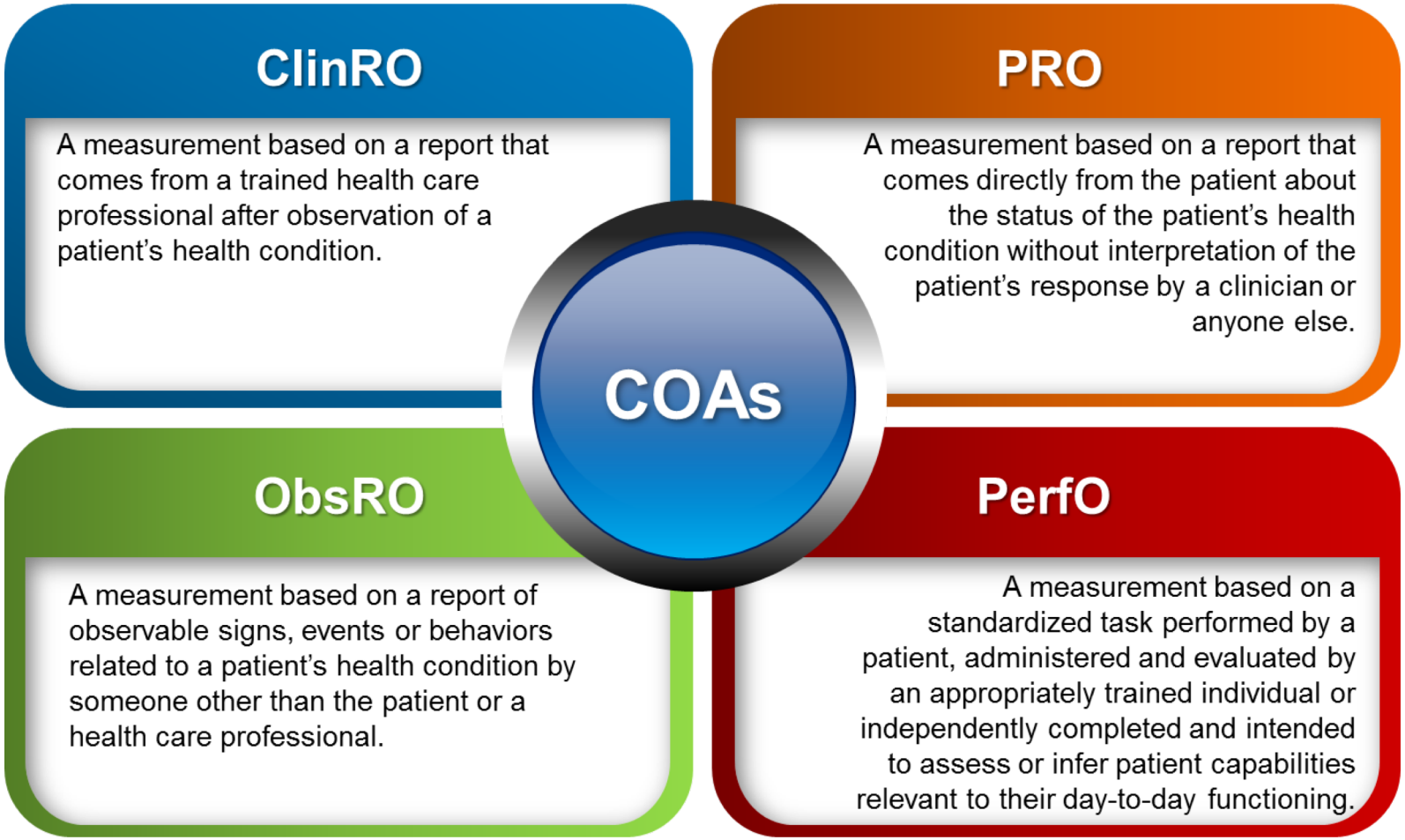
- What question are you asking?
  - Early phase development: **Is the drug active?**
  - Late phase development: **Does it provide clinical benefit?**

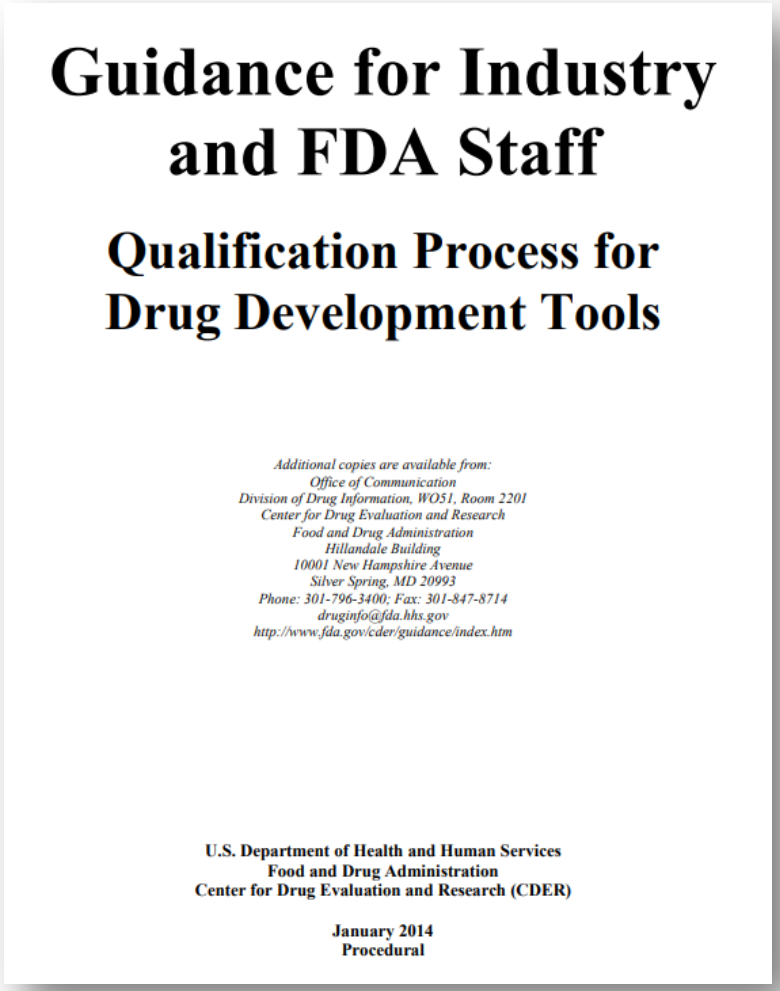
Regulatory Considerations

- **Treatment Benefit:** evidence of positive impact on a meaningful concept of interest - disease-related symptoms, function in daily life, survival
- **Measures of direct clinical benefit:**
  - Feels/Functions/Survives
- **Other/Surrogate Endpoints:**
  - *reasonably likely* to predict clinical benefit
  - Durable response rate, time to progression, progression-free survival

MEASURING TREATMENT BENEFIT

Clinical Outcomes Assessment Types





Guidance for Industry and FDA Staff

Qualification Process for Drug Development Tools

Additional copies are available from:
Office of Communication
Division of Drug Information, WO51, Room 2201
Center for Drug Evaluation and Research
Food and Drug Administration
Hillandale Building
10001 New Hampshire Avenue
Silver Spring, MD 20993
Phone: 301-796-3400; Fax: 301-847-8714
druginfo@fda.hhs.gov
http://www.fda.gov/cder/guidance/index.htm

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

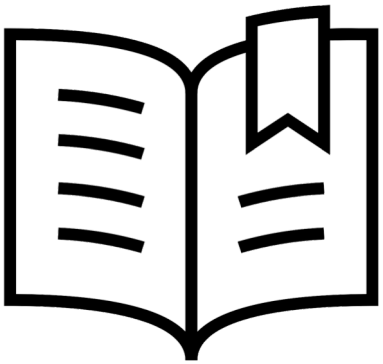
January 2014
Procedural

Outcomes

- Clinical Outcome Assessment Qualification Program (2014)

http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm230597.pdf

FDA PILOT
CLINICAL OUTCOME ASSESSMENT COMPENDIUM



Information Based on Drug Labeling Approved From 2003 to 2014: December 31, 2014; and CDER's DDT COA Qualification Program: December 31, 2015

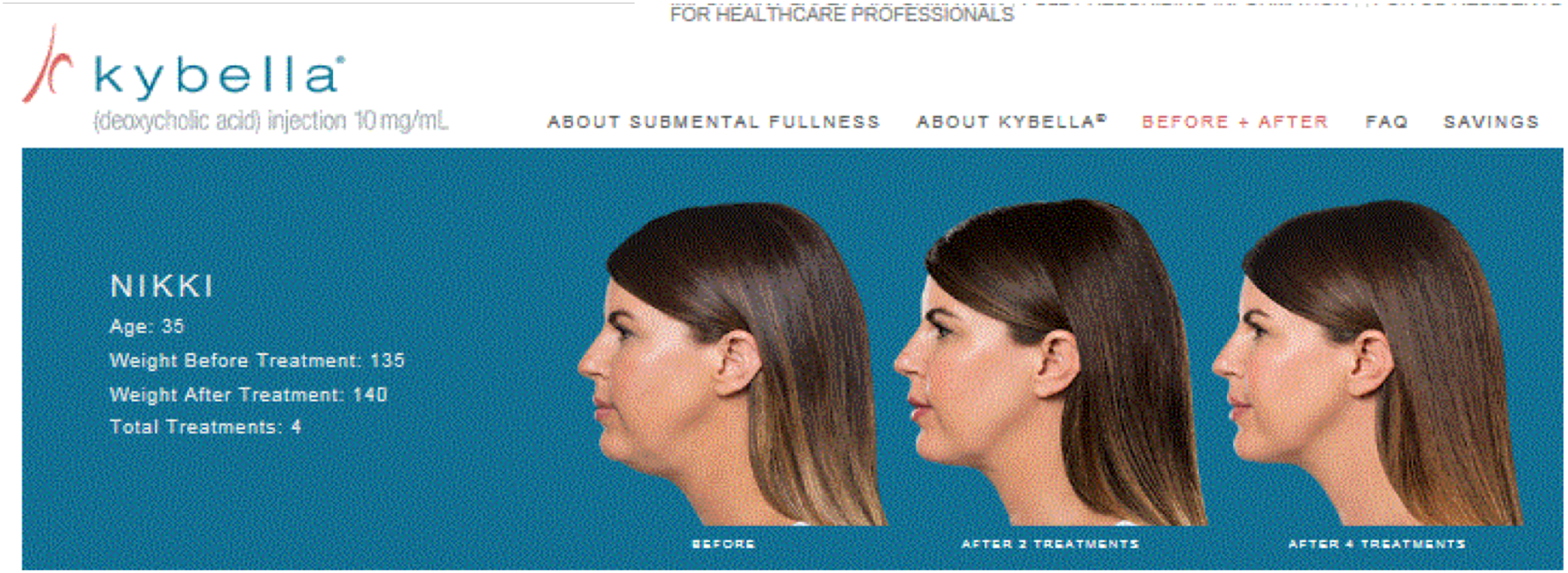
DERMATOLOGY AND DENTAL PRODUCTS

Disease/Condition	Indication and/or Claim(s) Description[30 31]	Outcome of Interest	COA (COA Type)	COA Context of Use	COA Qualification Information
Actinic keratosis (topical therapy)	Treatment of actinic keratosis (face, scalp, trunk, and extremities)	Clearance of actinic keratosis lesions	Clinician-reported outcome	Adult patients with actinic keratosis	Not applicable
External genital and perianal warts (topical therapy)	Treatment of external genital and perianal warts	Clearance of external genital and perianal warts	Clinician-reported outcome	Adult patients with external genital and perianal warts	Not applicable
Head lice infestations (topical therapy)	Treatment of head lice infestations	Absence of live lice	Clinician-reported outcome	Pediatric and adult patients with head lice infestations	Not applicable
Interdigital tinea pedis, tinea cruris, tinea corporis (topical therapy)	Treatment of interdigital tinea pedis, tinea cruris, and/or tinea corporis	Clearance of signs and symptoms (e.g., erythema, scaling, and pruritus)	Clinician reported outcome Note: pruritus symptoms are assessed based on patient-reported outcome	Pediatric and/or adult patients with interdigital tinea pedis, tinea cruris, and/or tinea corporis	Not applicable
		Fungal culture and potassium hydroxide (KOH) tests	Laboratory measure (biomarkers)		
Onychomycosis (topical therapy)	Treatment of onychomycosis	Clinical evidence of the disease (absence of signs/symptoms)	Composite assessment of clinician-reported outcome and laboratory measures (biomarkers)	Adult patients with onychomycosis	Not applicable
		Fungal culture and potassium hydroxide (KOH) tests			

CASE EXAMPLE - AESTHETIC

Case Example: Kybella

- **Indication:** improvement in the appearance of moderate to severe convexity or fullness associated with submental fat in adults
- From Kybella website:



Case Example: Kybella

- **Indication:** improvement in the appearance of moderate to severe convexity or fullness associated with submental fat in adults
- **Evidence of support: Primary Endpoint**
  - Composite primary efficacy endpoint, defined as the proportion of subjects with at least a 2-grade improvement from screening to 12 weeks post-treatment on both, the clinician-reported submental fat rating scale and the patient-reported submental fat rating scale

Case Example: Kybella

Evidence of support: Primary Endpoint - Composite primary at least a 2-grade improvement from screening to 12 weeks post-treatment on both, the clinician-reported submental fat rating scale and the patient-reported submental fat rating scale

Table 3 Clinician-Reported Submental Fat Rating Scale

Score	Submental Fat Description
0	Absent Submental Convexity: No localized submental fat evident.
1	Mild Submental Convexity: Minimal, localized submental fat.
2	Moderate Submental Convexity: Prominent, localized submental fat.
3	Severe Submental Convexity: Marked, localized submental fat.
4	Extreme Submental Convexity.

Table 4 Patient-Reported Submental Fat Rating Scale

*Please look in the mirror at **the area under your chin** to help you answer the following question: How much fat do you have under your chin right now?*

Mark ☒ in 1 box below

- ☐ No chin fat at all
- ☐ A slight amount of chin fat
- ☐ A moderate amount of chin fat
- ☐ A large amount of chin fat
- ☐ A very large amount of chin fat

Case Example: Kybella

Evidence of support: Primary Endpoint supported by secondary endpoints of:

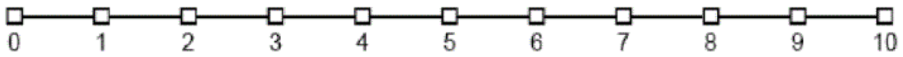
- Proportion of subjects who achieve at least 10% reduction in submental volume from baseline to 12 weeks post-treatment as assessed by MRI
- Change from baseline to 12 weeks post-treatment in patient-reported submental fat impact score

Table 9 Patient-Reported Submental Fat Impact Scale (PR-SMFIS)

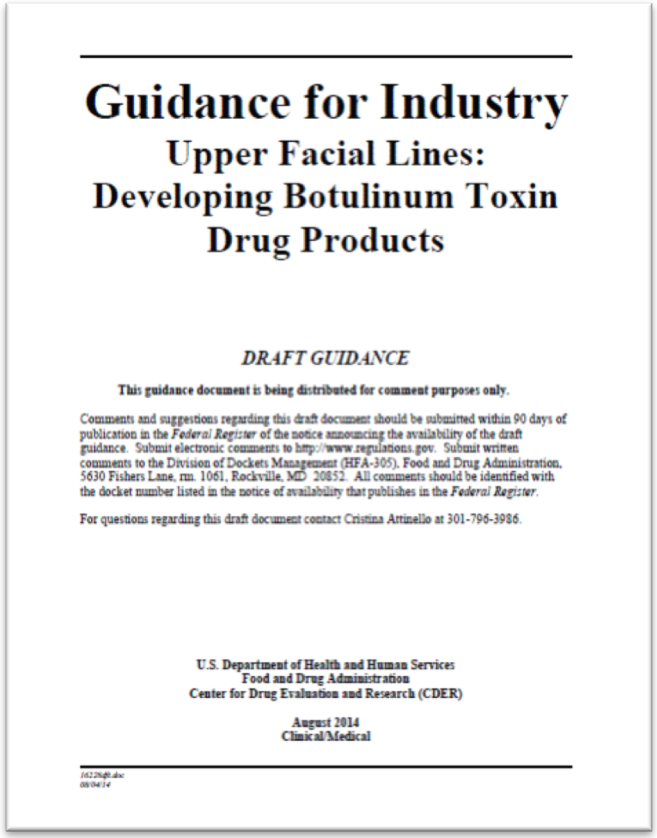
Please look in the mirror at the area under your chin to help you answer the following questions:

How happy are you with the appearance of your chin fat?
How bothered are you by the appearance of your chin fat?
How self-conscious are you about the appearance of your chin fat?
How embarrassed are you about the appearance of your chin fat?
How much older do you look because of your chin fat?
How much overweight do you look because of your chin fat?

The answers were recorded on 11-point horizontal scale going from Not at all (0) to Extremely (10)



A Pathway for Aesthetic Indications



Guidance for Industry

Upper Facial Lines: Developing Botulinum Toxin Drug Products

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 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 Division of Dockets Management (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 Cristina Attinello at 301-796-3986.

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

August 2014
Clinical/Medical

https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm407983.pdf

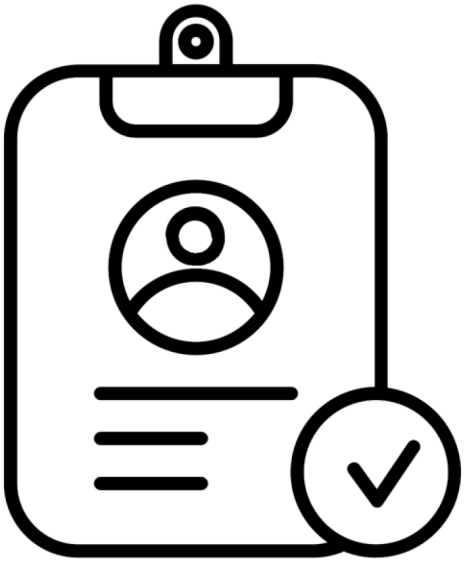
- Describes Agency's current thinking regarding drug development and trial design related to botulinum toxin and upper facial lines.
- Development programs with aesthetic aspects may benefit from the considerations described in the guidance.

What matters to patients?

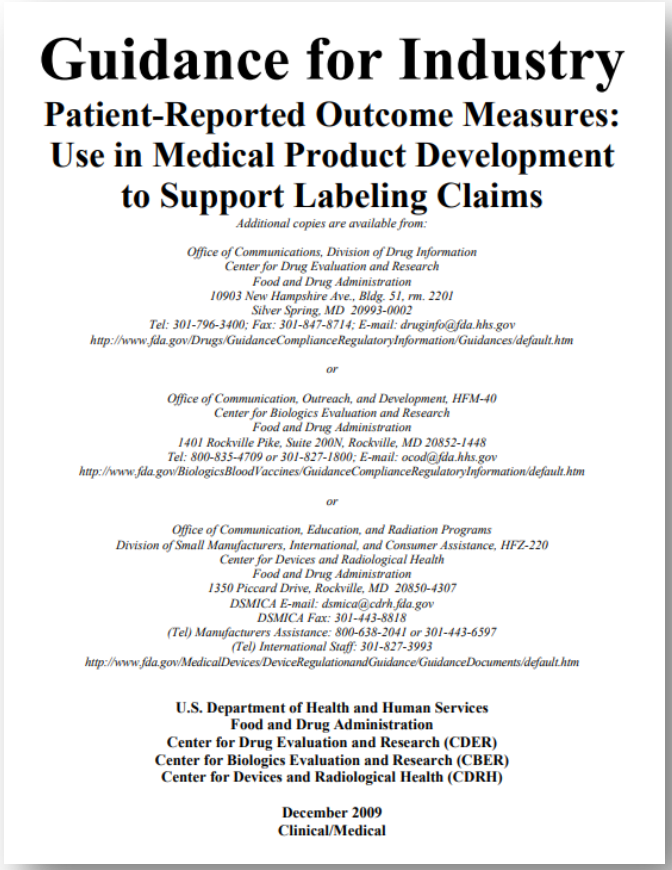
PATIENT REPORTED OUTCOMES (PRO)

Patient-Reported Outcome (PRO)

- A measurement based on a report that comes directly from the patient about the status of a patient's health condition *without amendment or interpretation* of the patient's response by a clinician or anyone else.
- Advised when measuring a concept best known by the patient
  - Examples: pain intensity, pruritus, asthma symptoms, rescue medication use, health-related quality of life



Good Measurement Principles



Guidance for Industry

Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims

Additional copies are available from:

Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 51, rm. 2201
Silver Spring, MD 20993-0002
Tel: 301-796-3400; Fax: 301-847-8714; E-mail: druginfo@fda.hhs.gov
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

or

Office of Communication, Outreach, and Development, HFM-40
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448
Tel: 800-835-4709 or 301-827-1800; E-mail: ocod@fda.hhs.gov
http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/default.htm

or

Office of Communication, Education, and Radiation Programs
Division of Small Manufacturers, International, and Consumer Assistance, HFZ-220
Center for Devices and Radiological Health
Food and Drug Administration
1350 Piccard Drive, Rockville, MD 20850-4307
DSMICA E-mail: dsmica@cdrh.fda.gov
DSMICA Fax: 301-443-8818
(Tel) Manufacturers Assistance: 800-638-2041 or 301-443-6597
(Tel) International Staff: 301-827-3993
http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/default.htm

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)
Center for Devices and Radiological Health (CDRH)

December 2009
Clinical/Medical

- Defines how the Agency interprets "well-defined and reliable" (21 CFR 314.126) for PRO measures intended to provide evidence of treatment benefit
- All COAs can benefit from the good measurement principles described in the PRO Guidance (i.e., valid, reliable, sensitive to change)
- But, flexibility and judgment are needed to meet practical demands!

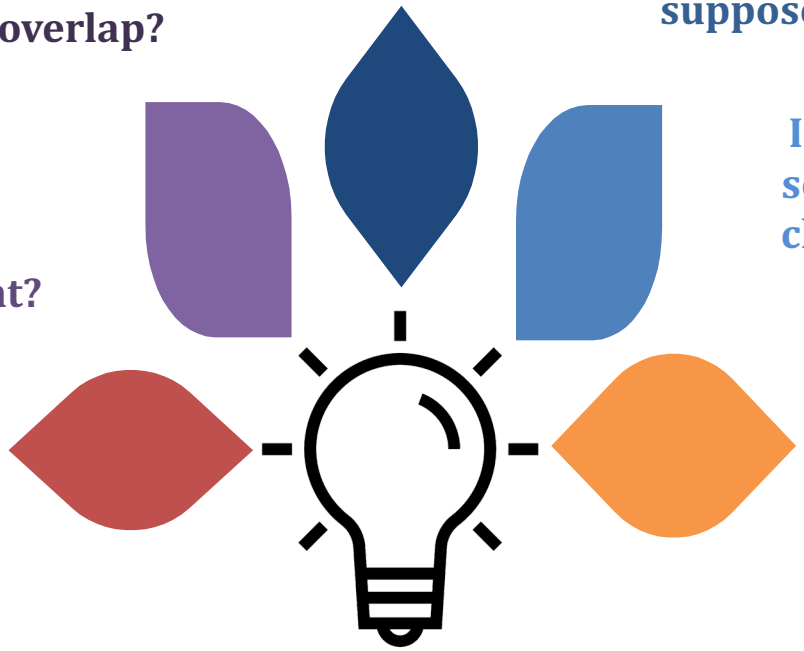
http://www.fda.gov/downloads/Drugs/Guidances/UCM193282.pdf

Good Measurement Principles

Is the instrument reliable?

If there are multiple concepts/domains being measured, do they overlap?

Does the instrument measure what it is supposed to measure?



Does the instrument measure what is important to the patient?

Is the instrument sensitive to detect change over time?

Did a subset of questions drive the result?

Is the instrument appropriate for use in the study population?

What does a score improvement of X-points mean?

Key Characteristics to Be Evaluated

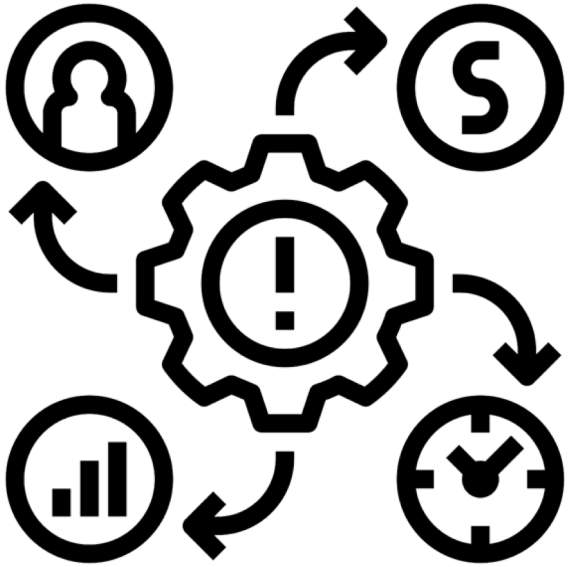
- Content Validity
- Psychometric Properties
  - Reliability
    - Test-retest or intra-rater reliability
    - Internal consistency reliability
    - Inter-rater reliability (*if appropriate*)
  - Validity
    - Construct Validity (known-groups validity; discriminant and convergent validity)
    - Ability to detect change
- Interpretation of Clinically Meaningful Change

Clinically Meaningful Change

Statistical significance alone is not sufficient.

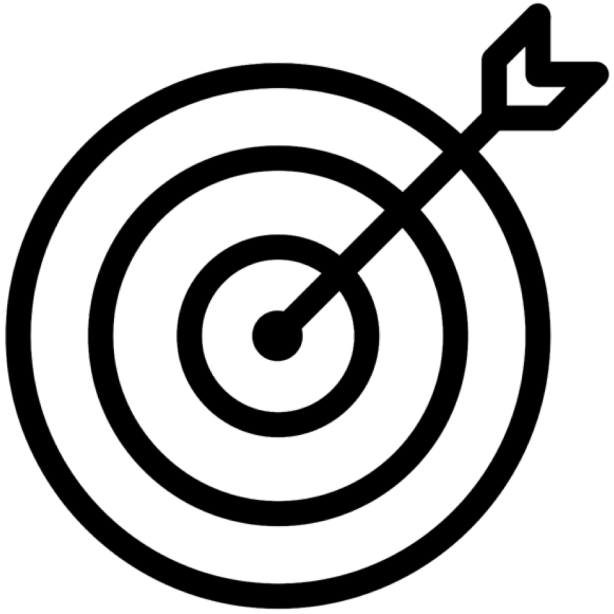
To establish clinical benefit we consider two questions:

1. Does the assessment measure or reflect something of significance to patients?
2. Is the magnitude of change at the individual level sufficiently large enough to affect how patients feel or function in daily life?



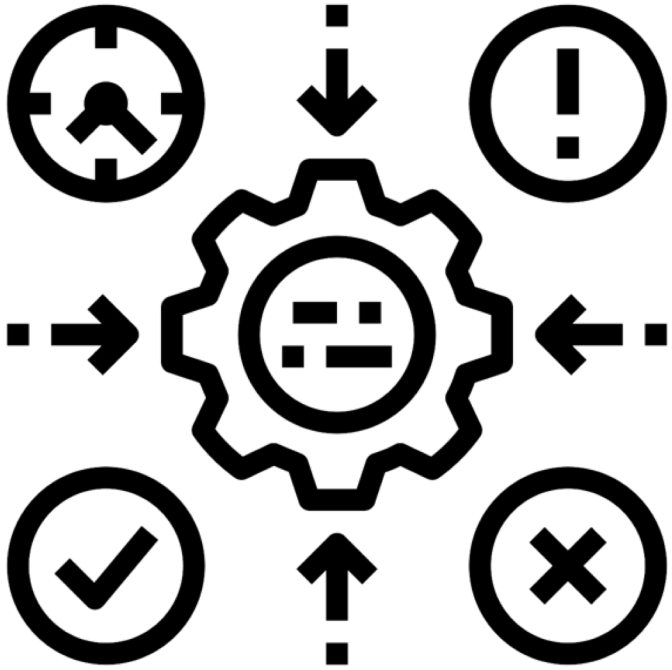
PRO Instrument Evaluation

- Clinical trial objectives and design
- Population enrolled
- PRO instrument conceptual framework
- PRO instrument measurement properties



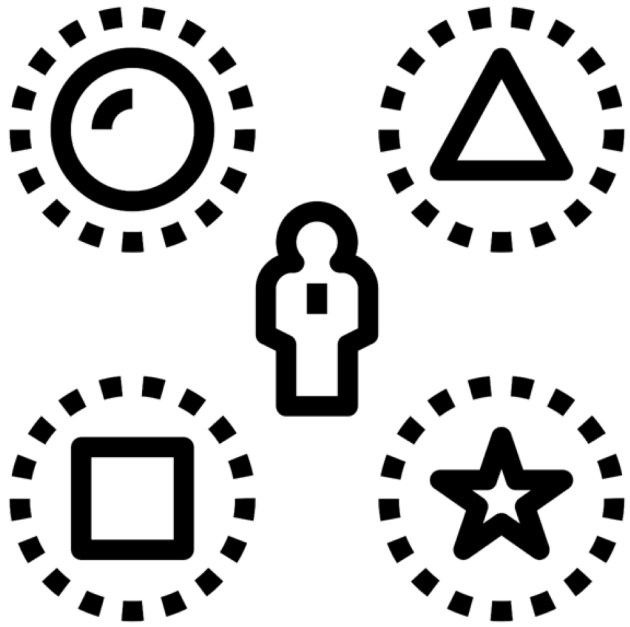
Evaluation of Characteristics

- Concepts
- Number of items
- Conceptual framework
- Medical condition/target population
- Data collection method
- Administration method
- Response options
- Recall period
- Scoring
- Weighting of items or domains
- Format
- Respondent burden
- Availability of cultural adaptation

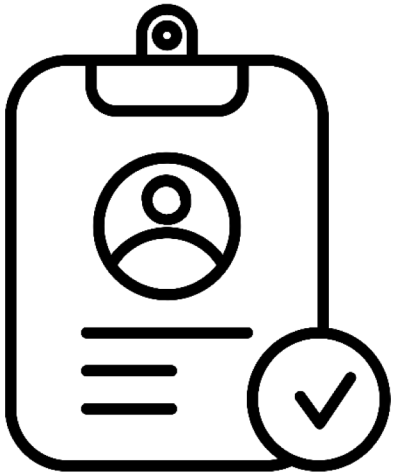


Common Reasons for Changing Items

- Lack of clarity or relevance
- Response range
- Lack of variability
- Lack of reproducibility
- Redundancy of items
- Item does not correlate with concept it is intended to measure
- Recall period



Examples: Patient Reported Outcomes



- Dermatology Life Quality Index (DLQI)
- Numerical Rating Scale – itch
- Average Axillary Sweating Daily Diary (ASDD) item #2

Dermatology Life Quality Index (DLQI)

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick (✓) one box for each question.

1.	Over the last week, how **itchy**, **sore**, **painful** or **stinging** has your skin been?	Very much A lot A little Not at all	❒ ❒ ❒ ❒
2.	Over the last week, how **embarrassed** or **self conscious** have you been because of your skin?	Very much A lot A little Not at all	❒ ❒ ❒ ❒
3.	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden**?	Very much A lot A little	❒ ❒ ❒
7.	Over the last week, has your skin prevented you from **working** or **studying**?	Yes No	❒ ❒ Not relevant ❒
	If "No", over the last week how much has your skin been a problem at **work** or **studying**?	A lot A little Not at all	❒ ❒ ❒
8.	Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒ Not relevant ❒
9.	Over the last week, how much has your skin caused any **sexual difficulties**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒ Not relevant ❒
10.	Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	Very much A lot A little Not at all	❒ ❒ ❒ ❒ Not relevant ❒

Please check you have answered EVERY question. Thank you.

1. Over the last week, how **itchy**, **sore**, **painful** or **stinging** has your skin been?

Very much ❒
A lot ❒
A little ❒
Not at all ❒

SCORING

Only for Adults >16+

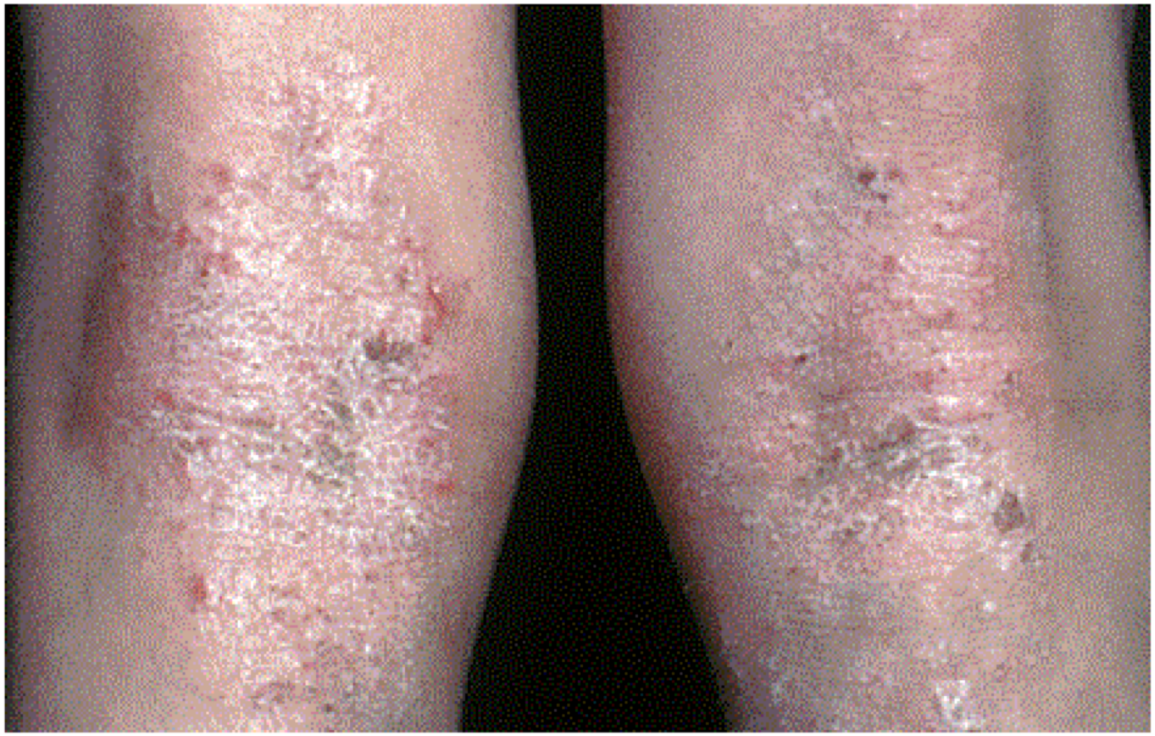
HOW TO INTERPRET MEANING OF DLQI SCORES

0	1	no effect at all on patient's life
2	5	small effect on patient's life
6	10	moderate effect on patient's life
11	20	very large effect on patient's life
21	30	extremely large effect on patient's life

Finlay and Khan Clin Exp Dermatol 1994

Atopic Dermatitis

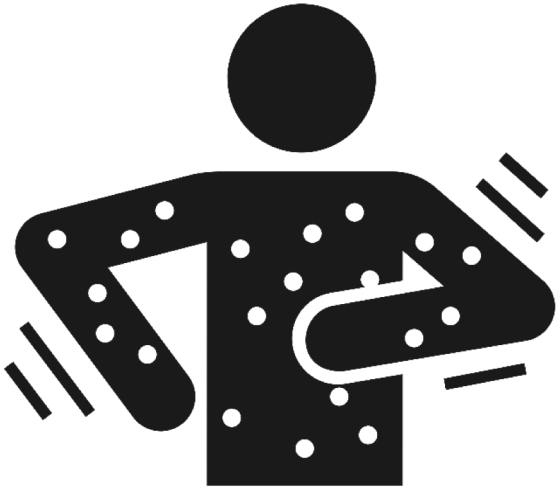
- Chronic, inflammatory disease of the skin
- Itch-scratch cycle



American Academy of Dermatology website

The Peak Pruritus Numerical Rating Scale (NRS)

"On a scale of 0 to 10, with 0 being 'no itch' and 10 being the 'worst itch imaginable', how would you rate your itch overall (on average) during the previous 24 hours?"



Baseline: 3 or more
Responder: at least 4-point improvement

The Peak Pruritus Numerical Rating Scale (NRS)

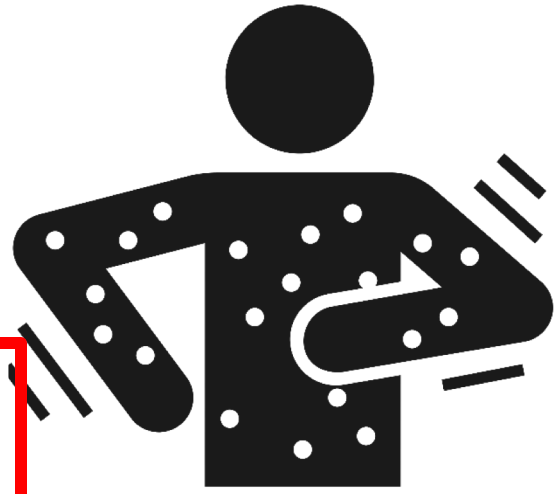
Table 3: Efficacy Results of DUPIXENT With or Without Concomitant TCS at Week 16 (FAS)

	Trial 1		Trial 2		Trial 3	
	DUPIXENT 300 mg Q2W	Placebo	DUPIXENT 300 mg Q2W	Placebo	DUPIXENT 300 mg Q2W + TCS	Placebo + TCS
Number of subjects randomized (FAS)[a]	224	224	233	236	106	315
IGA 0 or 1[b,c]	38%	10%	36%	9%	39%	12%
EASI-75[c]	51%	15%	44%	12%	69%	23%
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Number of subjects with baseline Peak Pruritus NRS score ≥4	213	212	225	221	102	299
Peak Pruritus NRS (≥4-point improvement)[c]	41%	12%	36%	10%	59%	20%

[a] Full analysis Set (FAS) [illegible] all subjects randomized.

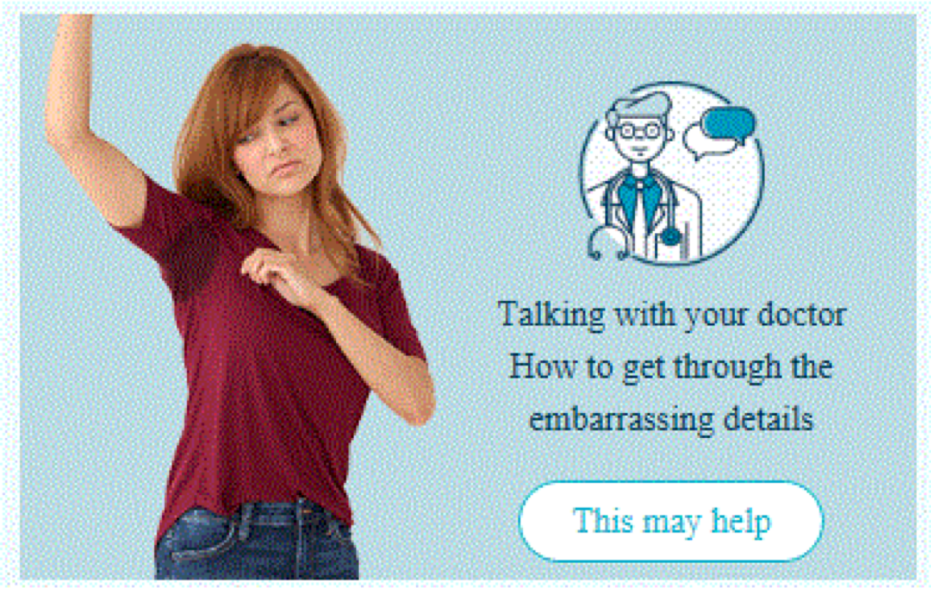
[b] Responder was defined as a subject with IGA 0 or 1 ("clear" or "almost clear") with a reduction of ≥2 points on a 0-4 IGA scale.

[c] Subjects who received rescue treatment or with missing data were considered as non-responders.



Primary Axillary Hyperhidrosis

- Excessive sweating of the armpits, not due to other medical problems
- Excessive – more than necessary



Qbrexza website

Axillary Sweat Daily Diary, Item #2

- **Indication:** topical treatment of primary axillary hyperhidrosis in adults and pediatric patients 9 years of age and older

Figure 1: Axillary Sweating Daily Diary (ASDD) Item #2

2. **During the past 24 hours**, how would you rate your underarm sweating **at its worst?**

☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
0	1	2	3	4	5	6	7	8	9	10
No sweating at all										Worst possible sweating

Baseline: 4 or more
Responder: at least 4-point improvement

Axillary Sweat Daily Diary, Item #2

- **Indication:** topical treatment of primary axillary hyperhidrosis in adults and pediatric patients 9 years of age and older

Figure 2: Axillary Sweating Daily Diary Children (ASDD-C)

These questions measure how bad your underarm sweating was last night and today. Please think only about your underarm sweating when answering these questions. Please complete these questions each night before you go to sleep.

1. **Thinking about last night and today**, did you have **any** underarm sweating?

a) Yes

b) No

2. **Thinking about last night and today,** how **bad** was your underarm sweating?

☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
0	1	2	3	4	5	6	7	8	9	10
No sweating at all										Worst possible sweating

Qbrexza (glycopyrronium) review

Axillary Sweat Daily Diary, Item #2

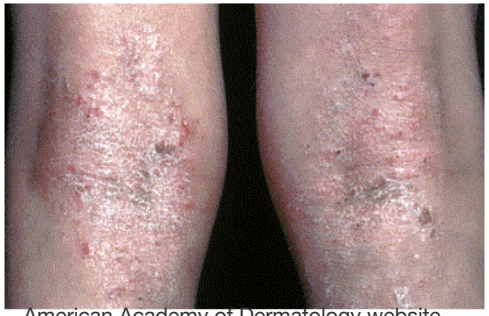
Table 5: Primary Efficacy Outcomes in Subjects with Primary Axillary Hyperhidrosis

	Trial 1		Trial 2	
	Qbrexza, 2.4% N = 229	Vehicle N = 115	Qbrexza, 2.4% N = 234	Vehicle N = 119
ASDD Item #2 Response at Week 4: Proportion of subjects with at least a 4-point improvement from baseline in the weekly mean ASDD item #2 at Week 4	53%	28%	66%	27%
Change from Baseline in Sweat Production at Week 4 (mg/5 minutes):				
Median	-81	-66	-79	-58
25th percentile, 75th percentile	-149, -40	-106, -28	-144, -45	-122, -21

CLINICIAN REPORTED OUTCOMES

Clinician Reported Outcomes

- CRO development parallels PRO development
- Investigator Global Assessment (IGA)



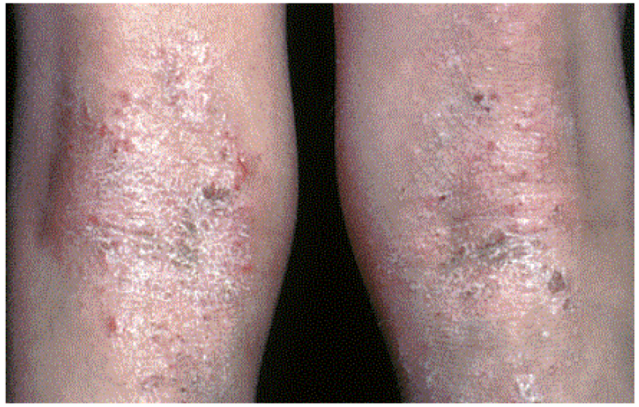
American Academy of Dermatology website

Table 6. Investigator's Global Assessment (IGA) Scale

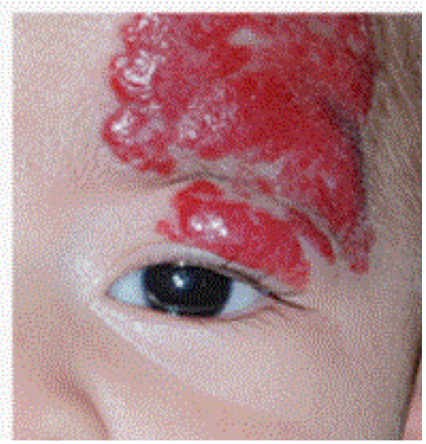
Score	Investigator's Global Assessment (IGA) Standard Definitions	Investigator's Global Assessment (IGA): Morphological Descriptors
0 = Clear	No inflammatory signs of atopic dermatitis	No inflammatory signs of atopic dermatitis
1 = Almost clear	Just perceptible erythema, and just perceptible papulation/infiltration	Barely perceptible erythema and/or minimal lesion elevation (papulation/infiltration)
2 = Mild disease	Mild erythema and mild papulation/infiltration	Visibly detectable, light pink erythema and very slight elevation (papulation/infiltration)
3 = Moderate disease	Moderate erythema and moderate papulation/infiltration	Dull red, clearly distinguishable erythema; clearly perceptible elevation (papulation/infiltration), but not extensive
4 = Severe disease	Severe erythema and severe papulation/infiltration	Deep/dark red erythema; marked and extensive elevation (papulation/infiltration)

Clinician Reported Outcomes

- Question: Is the IGA appropriate for the proposed disease indication
  - Inflammatory versus neoplastic process



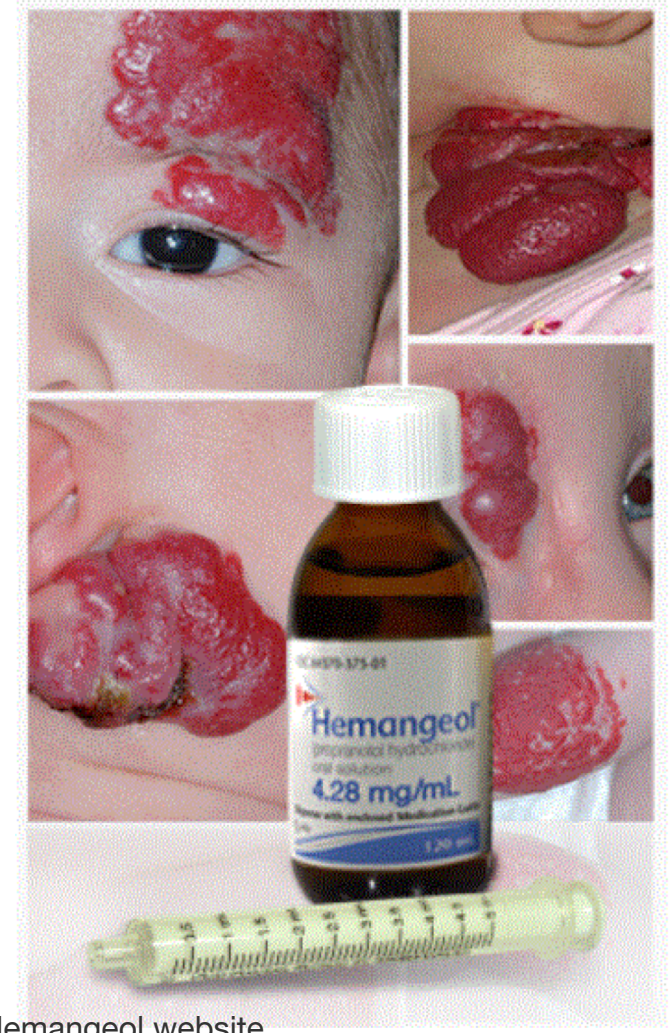
American Academy of Dermatology website



Hemangeol website

CASE EXAMPLE:
INFANTILE HEMANGIOMA

Infantile Hemangioma



Hemangeol website

- A benign vascular tumor, usually of skin
- Specific natural history
  - Usually faintly present at birth
  - Proliferation
  - Plateau
  - Involution

Case Example: Hemangeol

- **Indication:** treatment of proliferating infantile hemangiomas requiring systemic therapy, to be initiated in patients aged 5 weeks to 5 months
- **Evidence of support: Primary Endpoint**
  - The complete/nearly complete resolution of target IH from baseline to Week 24 based on blinded, centralized assessments of standardized photographs at Week 24 compared to those at baseline.
  - Nearly complete resolution: minimal degree of telangiectasia, erythema, skin thickening, soft tissue swelling, and/or distortion of anatomical landmarks

Case Example: Hemangeol

- **Evidence of support: Primary Endpoint**
  - The complete/nearly complete resolution of target IH from baseline to Week 24 based on blinded, centralized assessments of standardized photographs at Week 24 compared to those at baseline.

- **Secondary Endpoints**
  - On-site investigator assessment of resolution
  - On-site parent assessment of IH evolution

4 Key Points

- Consult the published FDA Guidelines
  - https://www.fda.gov/RegulatoryInformation/Guidances/default.htm
- Science – basic, clinical and regulatory - is continuously evolving
- Previous approvals can serve as a guiding post
  - https://www.fda.gov/scienceresearch/bioinformaticstools/ucm289739.htm
  - https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm
- FDA is available to provide additional guidance through appropriate pathways

Acknowledgements

- Kendall Marcus, MD
- Natalia Chalmers, DDS
- Denise Kelly, MD
- Hon-Sum Ko, MD

melissa.reyes@fda.hhs.gov

U.S. Food and Drug Administration