FDA Drug Topics: Safety Labeling Changes for Leukotriene Receptor Antagonists and Decisions Behind a Boxed Warning

Katherine Clarridge, MD, MSc
Division of Pulmonology, Allergy, and Critical Care
Office of Immunology and Inflammation
Office of New Drugs
Center for Drug Evaluation and Research



Objectives

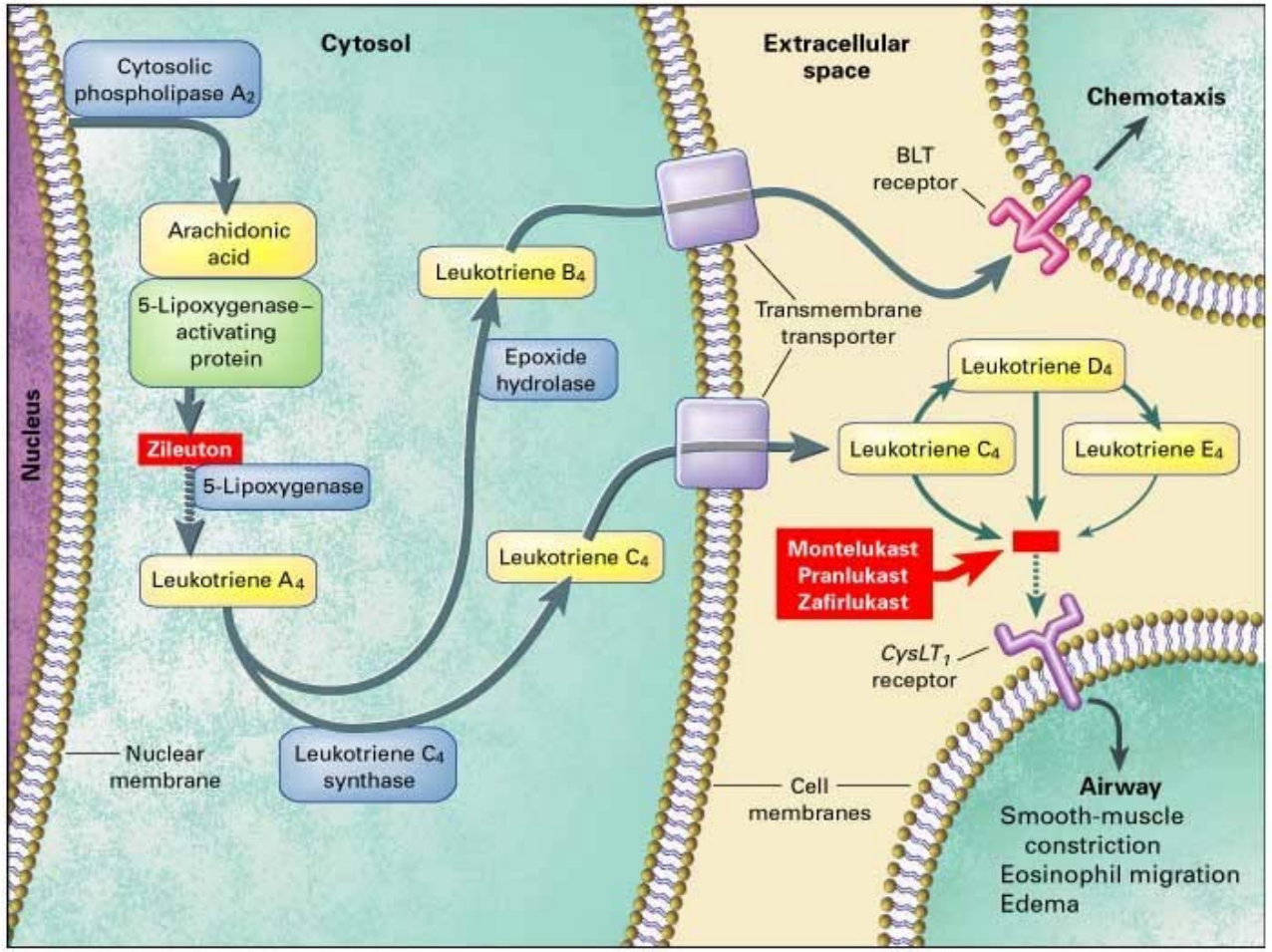
- Identify the spectrum of neuropsychiatric adverse events, including serious neuropsychiatric events associated with montelukast use.
- List the different sources of safety data that contributed to the understanding of the risk of neuropsychiatric events with montelukast.
- Describe the revised labeling recommendations for use of montelukast in patients with allergic rhinitis.

Outline

- **Product Information**
- Neuropsychiatric Events and Safety Labeling
- Regulatory History Related to Neuropsychiatric Findings
- Regulatory Considerations
- Decision Making
- Updated Safety Labeling
- Discussion Topics
- Challenge Questions

Leukotriene Receptor Antagonists (LTRAs)

- LTRAs
  - Montelukast
  - Zafirlukast
- 5-lipoxygenase inhibitors
  - Zileuton



Drazen JM, Israel E, O'Byrne PM. Treatment of asthma with drugs modifying the leukotriene pathway. N Engl J Med. 1999;340(3):197-206.

Product Information

- Montelukast
- Mechanism of Action: specific cysteinyl leukotriene type-1 receptor antagonist (CYSLT-1)
- Approved for:
  - prophylaxis and chronic treatment of asthma
  - seasonal or perennial allergic rhinitis
  - prevention of exercise-induced bronchoconstriction
- Approval History
  - Tablets 4, 5, 10 mg: approved February 1998
  - Chewable Oral Granules 4 mg: approved July 2002
- Multiple generic forms

Approved Montelukast Prescription Dosing by Indication and Age	
Indication/Age	**Dose**
Asthma	
≥ 15 years	10 mg
6-14 years	5 mg
12 months - 5 years	4 mg
Seasonal Allergic Rhinitis (SAR)	
≥ 15 years	10 mg
6-14 years	5 mg
2-5 years	4 mg
Perennial Allergic Rhinitis (PAR)	
≥ 15 years	10 mg
6-14 years	5 mg
6 months - 5 years	4 mg
Exercise-Induced Bronchoconstriction (EIB)	
≥ 15 years	10 mg
6-14 years of age	5 mg
Source: Prescription Package Insert	

Outline

- Product Information
- **Neuropsychiatric Events and Safety Labeling**
- Regulatory History Related to Neuropsychiatric Findings
- Regulatory Considerations
- Decision Making
- Updated Safety Labeling
- Discussion Topics
- Challenge Questions

Recent Safety Labeling Changes

- New Boxed warning
- Changed the indication for allergic rhinitis
- Expanded the Warnings and Precautions
- Created new Medication Guide

WARNING: SERIOUS NEUROPSYCHIATRIC EVENTS

See full prescribing information for complete boxed warning.

- **Serious neuropsychiatric events have been reported in patients taking (5.1).**
- **Discuss benefits and risks of with patients and caregivers (5.1).**
- **Monitor for neuropsychiatric symptoms in patients taking (5.1).**
- **Discontinue immediately if neuropsychiatric symptoms occur (5.1).**
- **Because the benefits of may not outweigh the potential risk of neuropsychiatric symptoms in patients with allergic rhinitis, reserve use for patients who have an inadequate response or intolerance to alternative therapies (1.3, 5.1).**

Safety Labeling Changes updated 4/2020

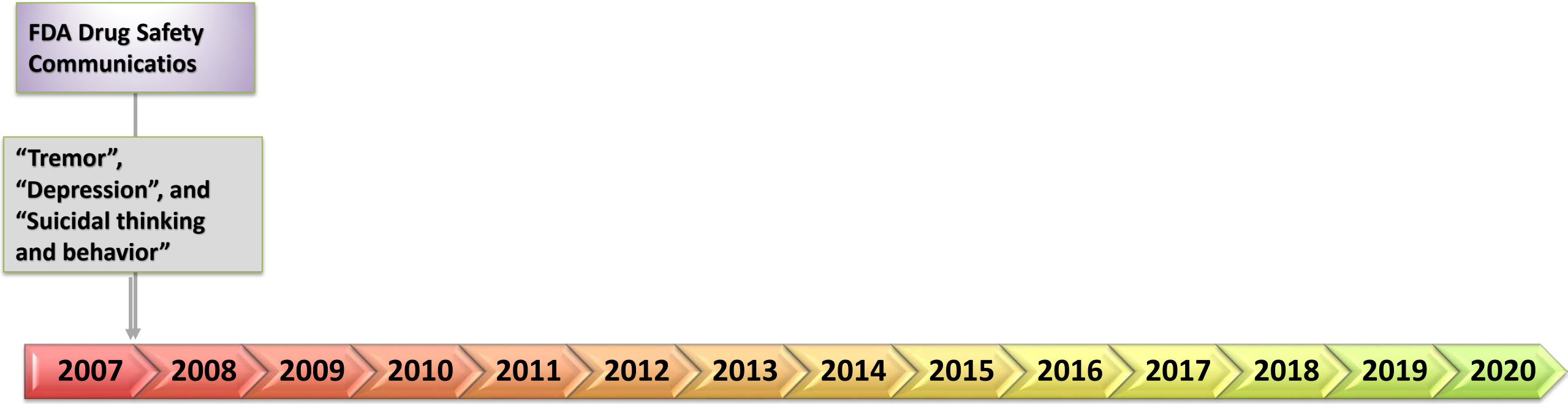
Outline

- Product Information
- Neuropsychiatric Events and Safety Labeling
- **Regulatory History Related to Neuropsychiatric Findings**
- Regulatory Considerations
- Decision Making
- Updated Safety Labeling
- Discussion Topics
- Challenge Questions

Regulatory History



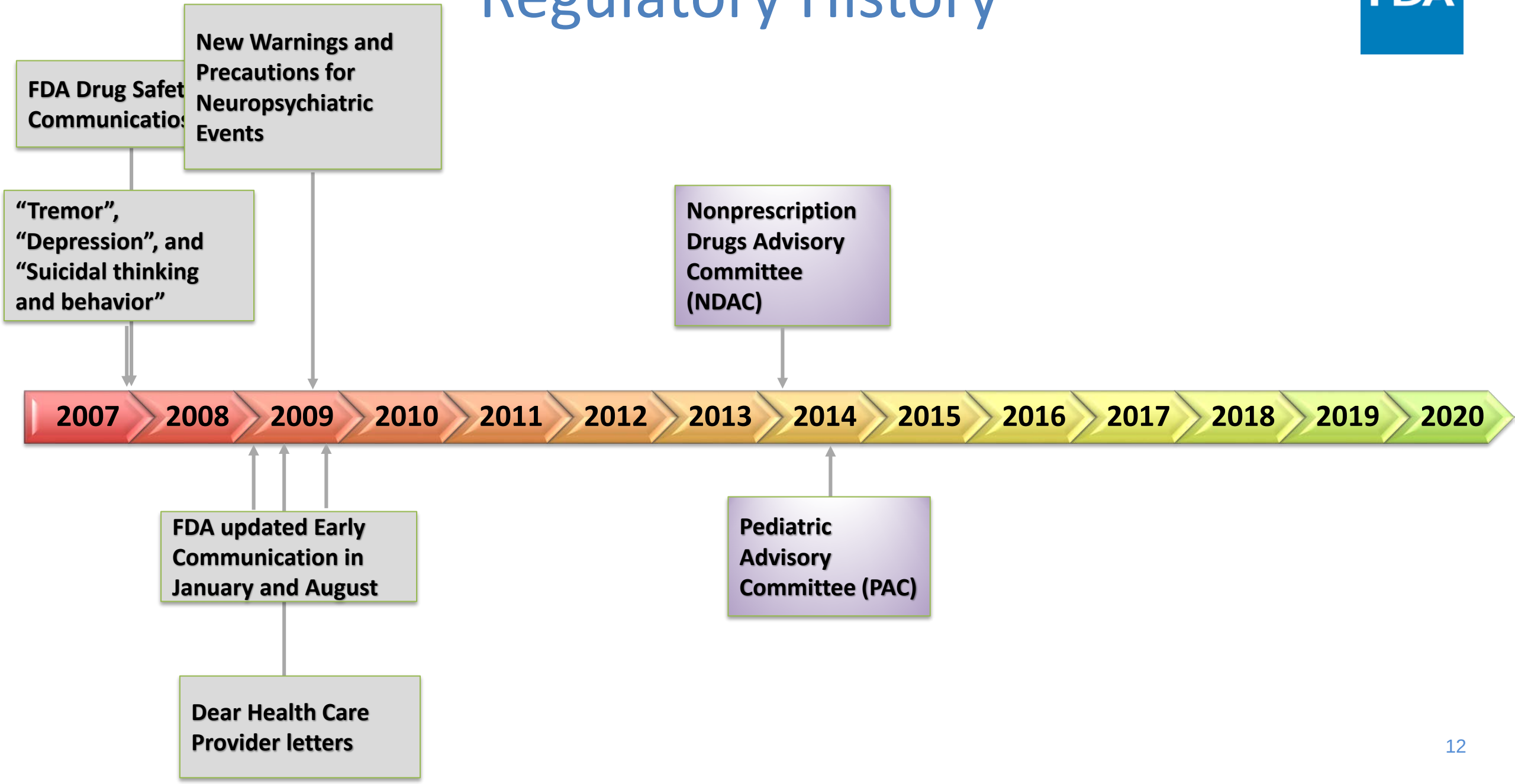
Regulatory History



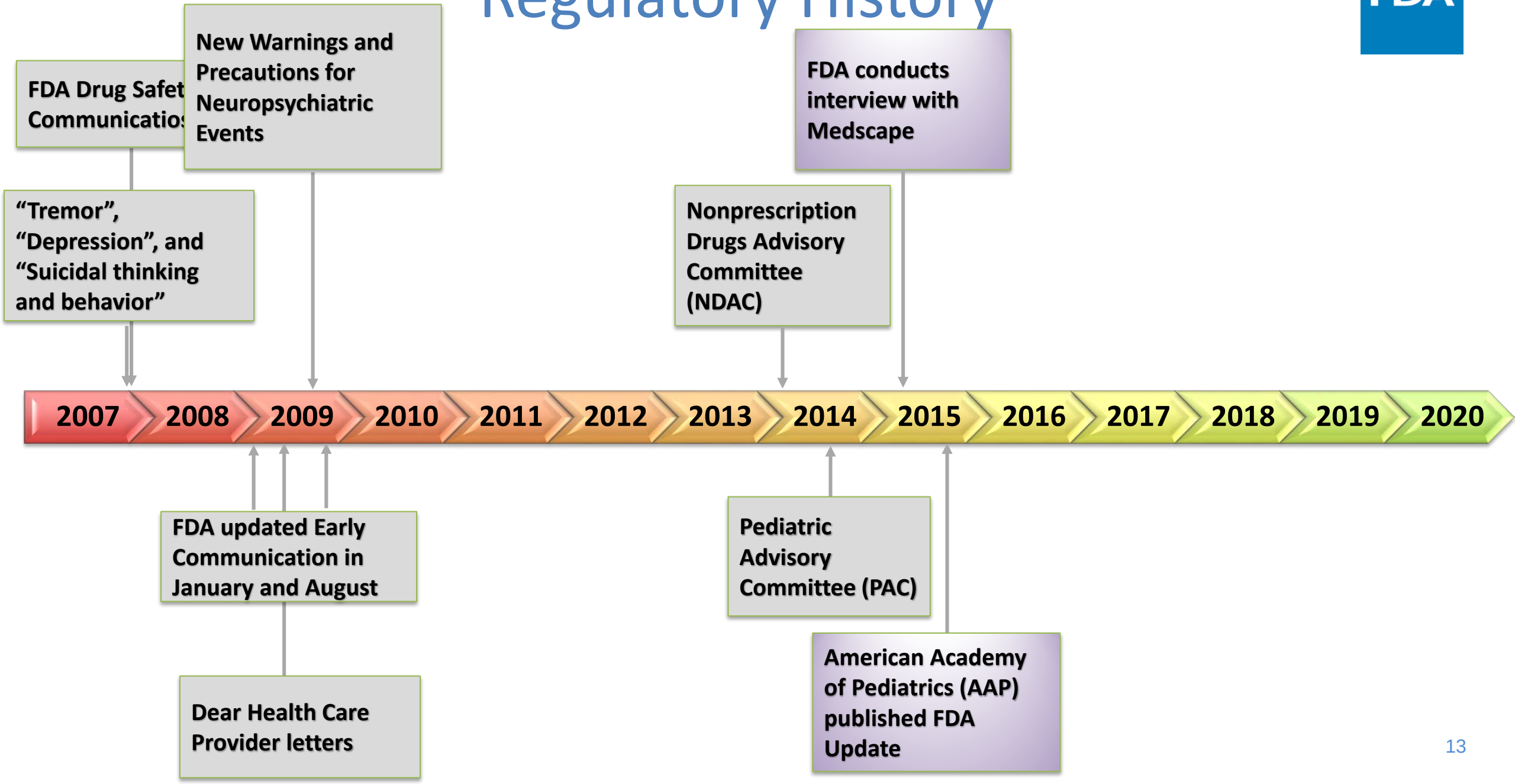
Regulatory History



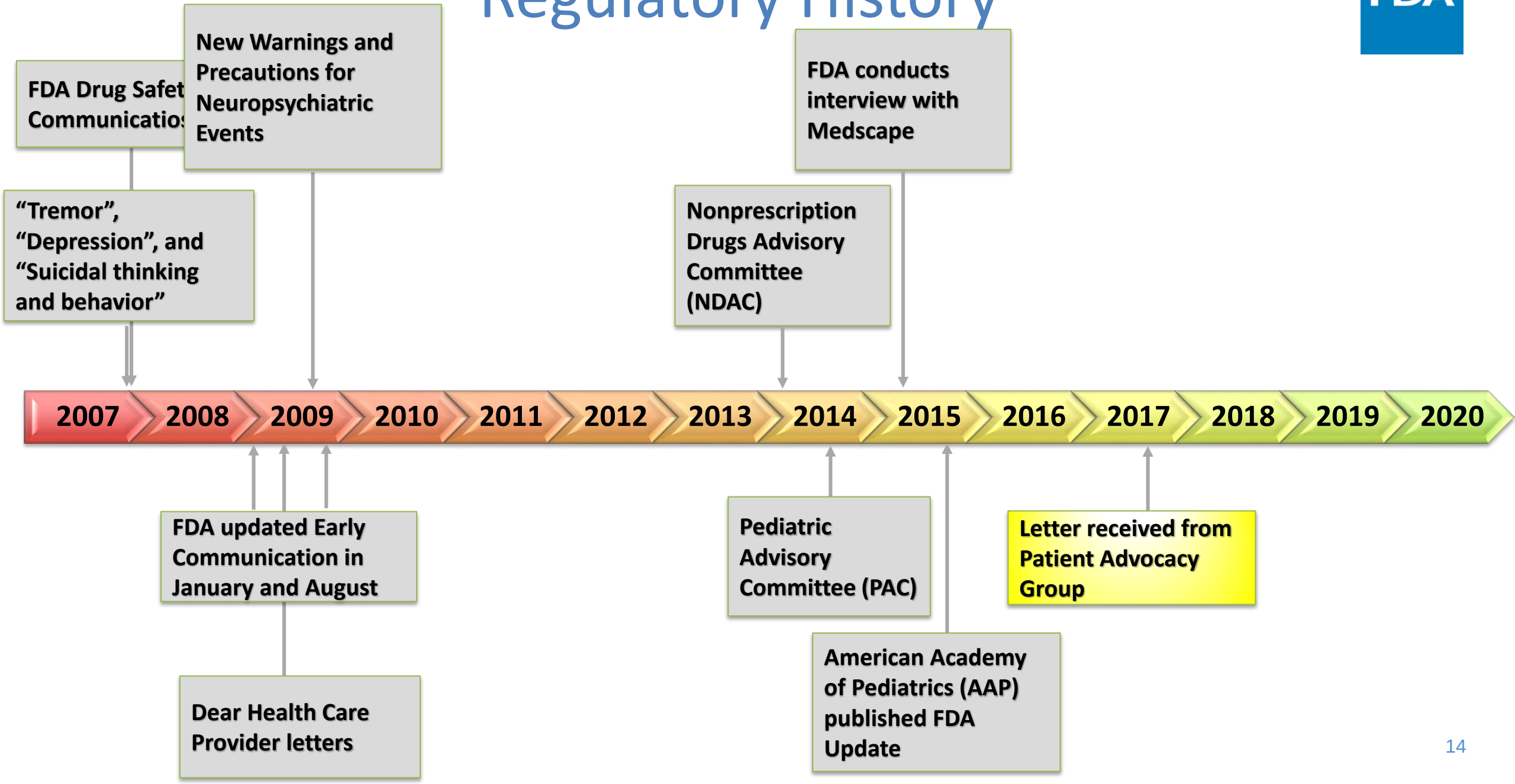
Regulatory History



Regulatory History



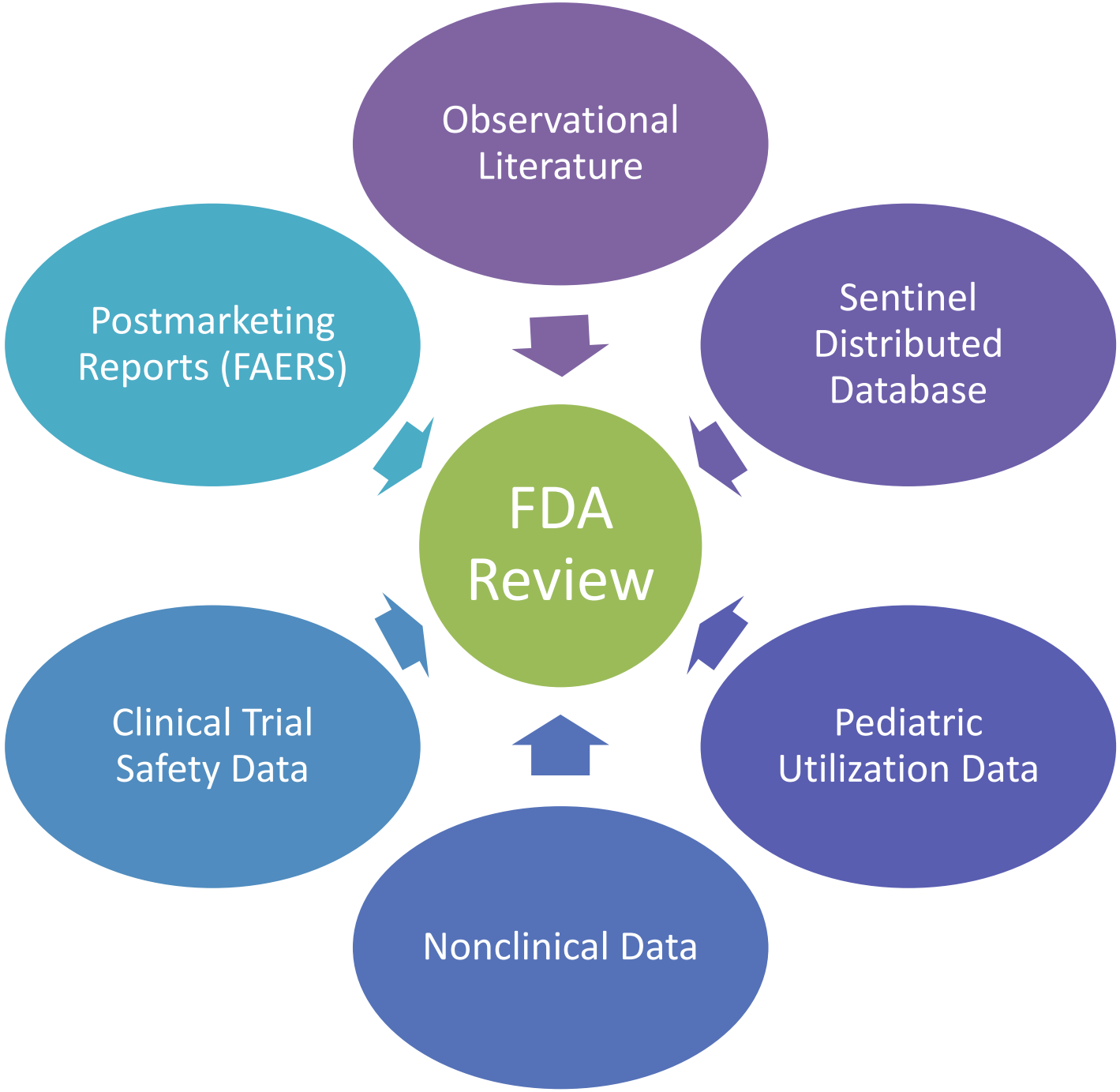
Regulatory History



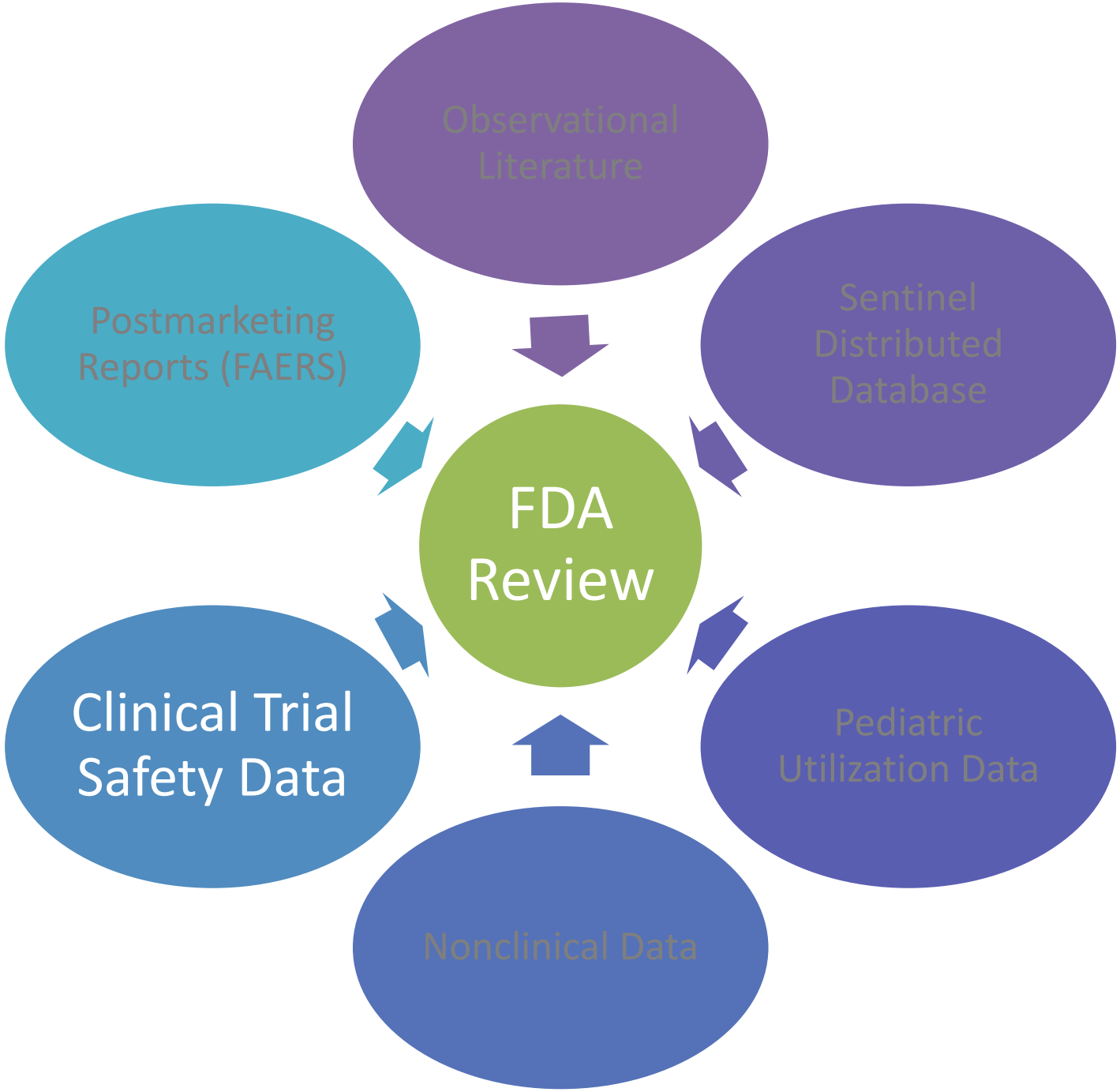
Stakeholder Letter from 2017

The letter requested the following from the FDA:

1) Determine the mechanisms for montelukast's neuropsychiatric side effects.
2) Determine the risk factors for neuropsychiatric adverse reactions.
3) Determine the appropriate way to discontinue montelukast.
4) Evaluate withdrawal symptoms and long-term sequelae of an adverse reaction.
5) Reclassify neuropsychiatric side effects of montelukast to be common in children.
6) Update labeling to include a warning for "excoriation", "hyperkinesia", and "obsessive-compulsive disorder".
7) Issue a Medication Guide for montelukast.
8) Consider a boxed warning.

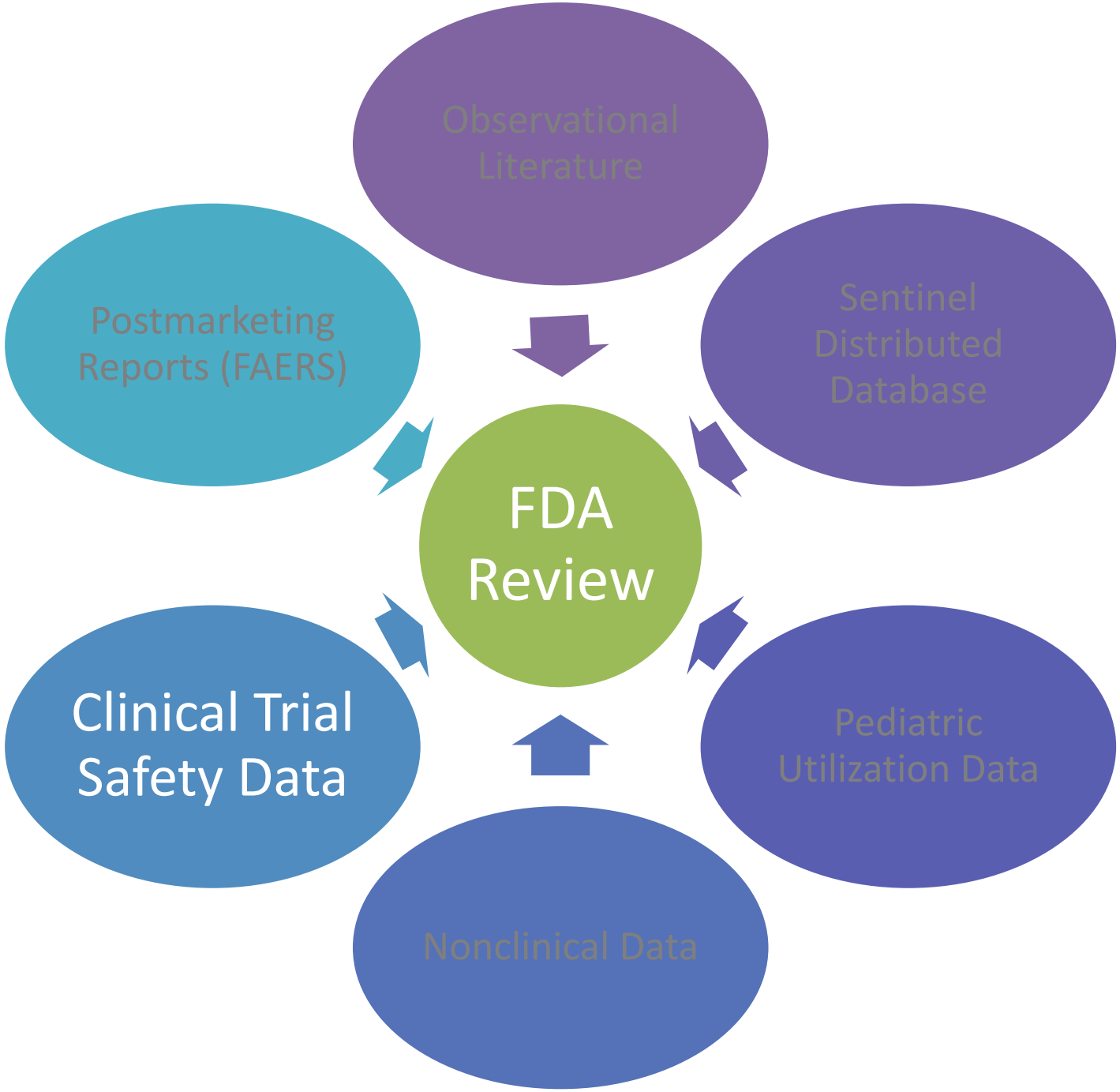


FDA Review of Neuropsychiatric (NP) Events


Observational Literature
Postmarketing Reports (FAERS)
Sentinel Distributed Database
FDA Review
Clinical Trial Safety Data
Pediatric Utilization Data
Nonclinical Data

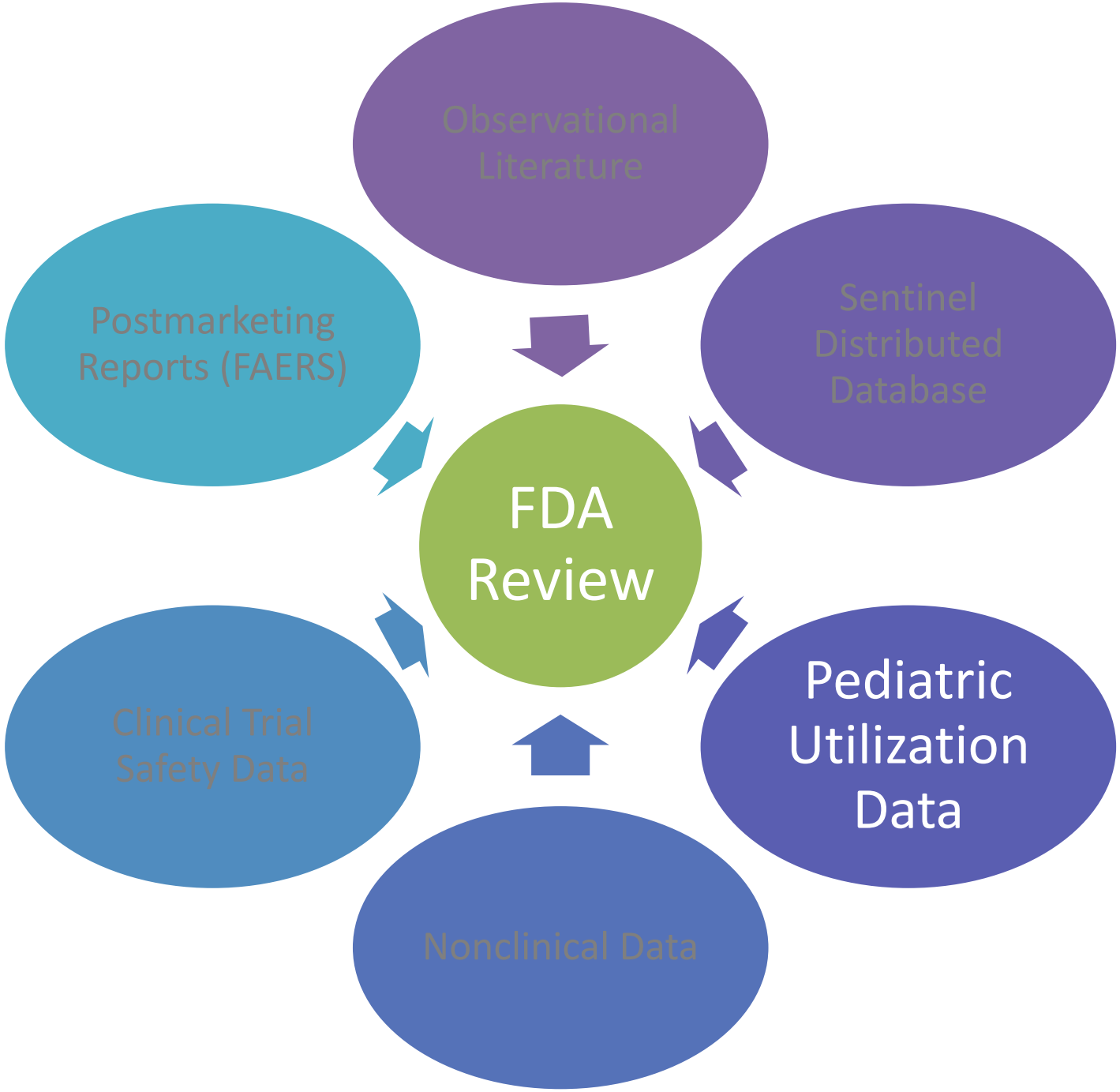
Clinical Trials To Support Approval

- Overall review did not reveal a strong signal for NP events
  - One adult patient (0.01%) out of 9929 patients treated with montelukast had suicidal ideation
  - Montelukast (2.8%) vs placebo (2.4%) for all NP events
- Size of the safety database varied for the individual indications
- The trials were generally short in duration
- Extrapolation used to extend indication to pediatric patients
- BUT trials not designed for NP events

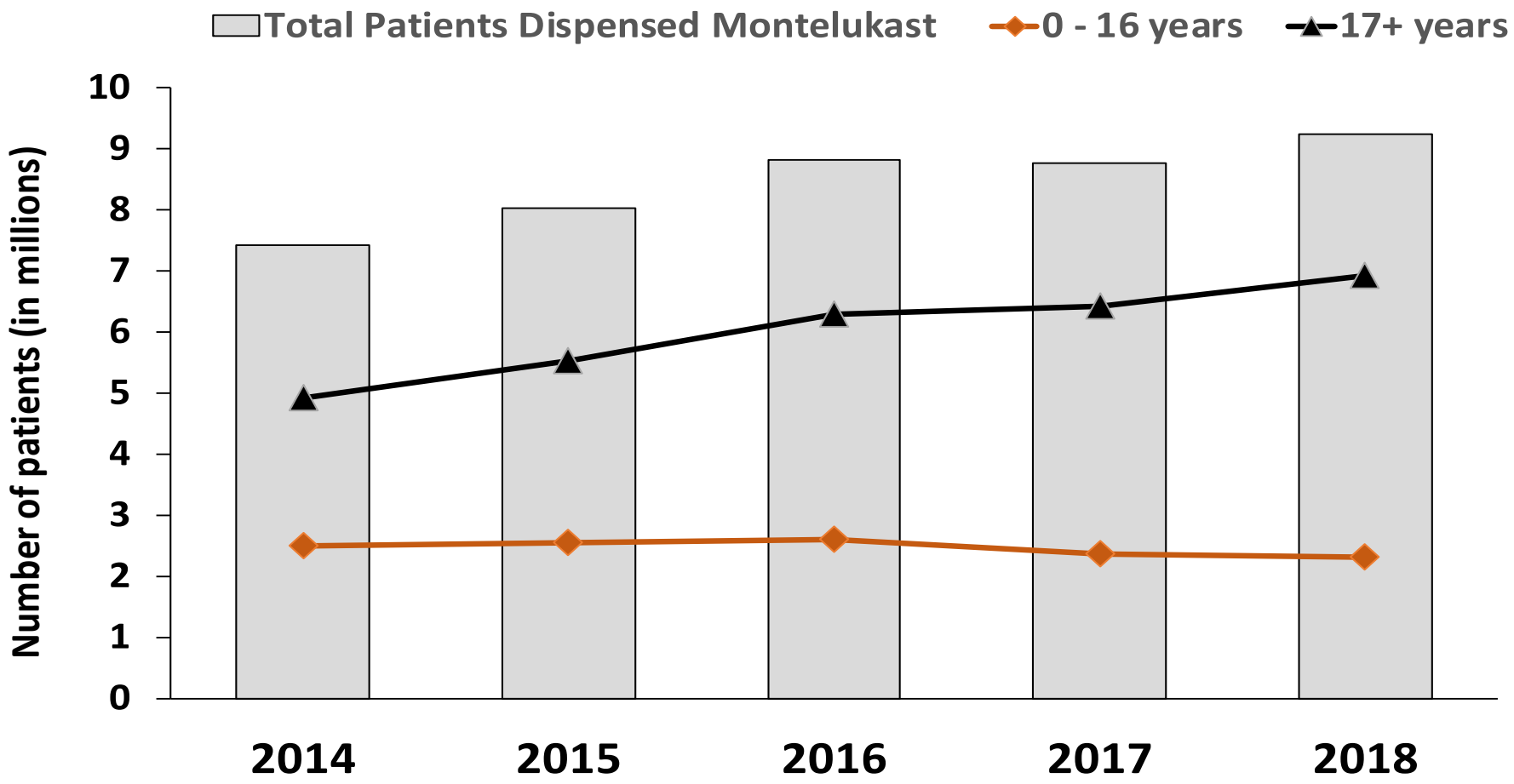


Conclusion:

- Lack of strong safety signal for neuropsychiatric events in the pre-market clinical trials
- Trials not designed for NP events

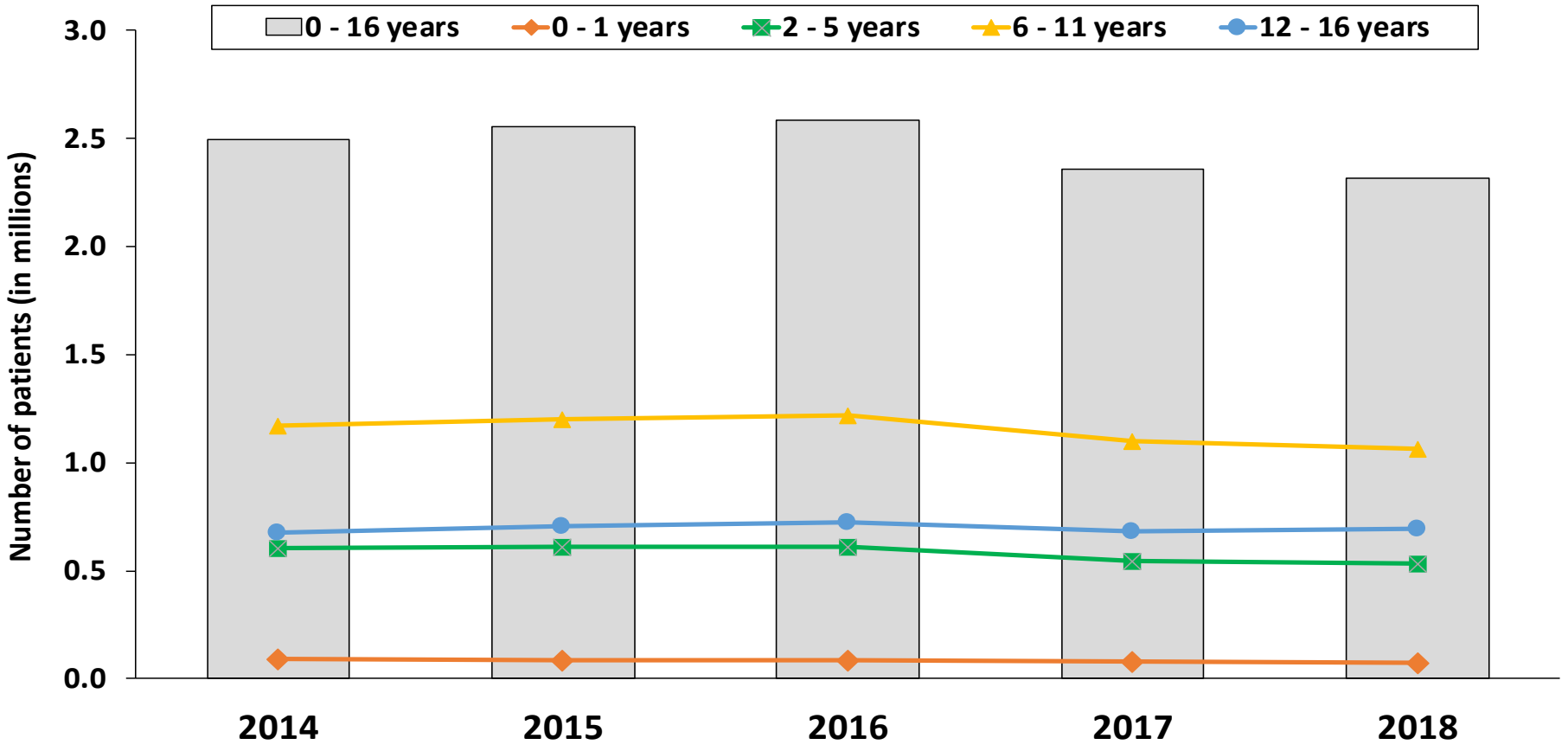

Observational Literature
Sentinel Distributed Database
Pediatric Utilization Data
Nonclinical Data
Clinical Trial Safety Data
Postmarketing Reports (FAERS)
FDA Review

Montelukast Utilization



National estimates of patients who received prescriptions dispensed for montelukast, by patient age, from U.S. outpatient retail pharmacies, 2014-2018. Data Source: IQVIA Total Patient Tracker™ 2014-2018. Extracted March 2019. Analysis performed by the Office of Surveillance and Epidemiology.

Pediatric Montelukast Utilization



National estimates of pediatric patients (0-16 years old) who received prescriptions dispensed for montelukast, stratified by patient age, from U.S. outpatient retail pharmacies, 2014-2018. Data Source: IQVIA Total Patient Tracker™ 2014-2018. Extracted March 2019. Analysis performed by the Office of Surveillance and Epidemiology.

Top Diagnosis Associated with Product use in Pediatric Patients

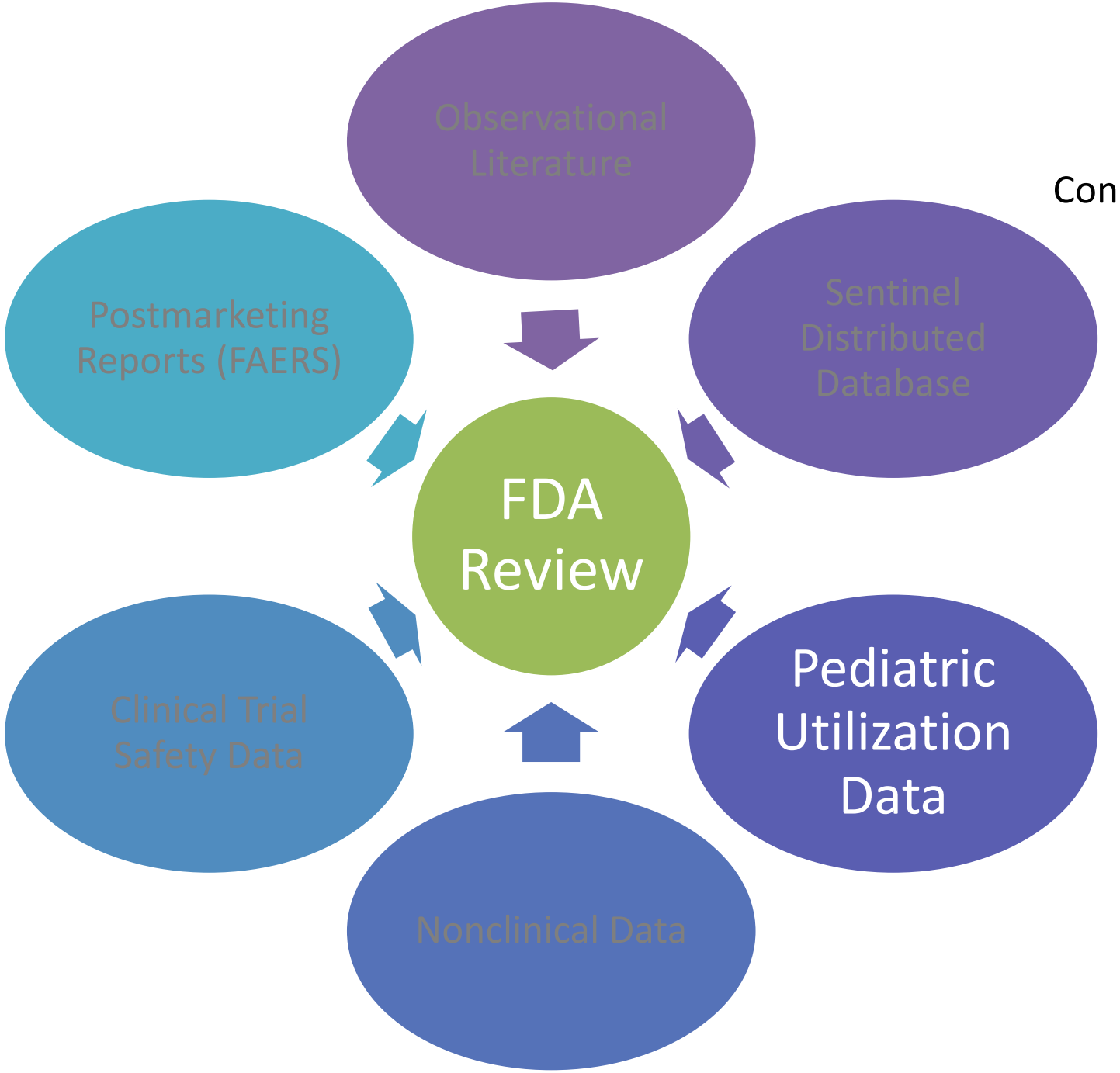
- <2 years old
  - Cough (45%)
  - Vasomotor and allergic rhinitis (33%)
  - Asthma (20%)
- 2 - 5 years old
  - Asthma (56%)
  - Vasomotor and allergic rhinitis (29%)
  - Cough (9%)
- 6 - 11 years old
  - Asthma (43%)
  - Vasomotor and allergic rhinitis (38%)
  - Encounter for general adult medical examination without abnormal findings (7%)
- 12-16 years old
  - Asthma (58%)
  - Vasomotor and allergic rhinitis (19%)
  - Cough (6%)

Top diagnoses associated with the use of Montelukast in pediatric patients (<2, 2-5, 6-11, 12-16 years old) as reported by U.S. office-based physician surveys, 2018. Source: Syneos Health Research & Insights LLC., TreatmentAnswers™. 2014-2018. Extracted February 2019. Analysis performed by the Office of Surveillance and Epidemiology.

Top Prescribing Specialties

	2018	
	TRxs	%
Total Prescriptions Dispensed for Montelukast	**35,400,841**	**100.0%**
Family Practice/General Practice/Internal Medicine	*12,126,035*	*34.3%*
Physician Assistants/Nurse Practitioners	*8,120,006*	*22.9%*
Pediatrics/Internal Medicine Pediatrics	*3,968,325*	*11.2%*
Osteopathic Medicine	*3,171,214*	*9.0%*
Allergy	*3,097,499*	*8.8%*
Pulmonary Diseases	*1,479,090*	*4.2%*
Otolaryngology	*1,084,295*	*3.1%*
Pulmonary Critical Care	*732,305*	*2.1%*
Geriatrics	*134,765*	*0.4%*
All other Specialties	*1,487,307*	*4.2%*

Source: IQVIA National Prescription Audit™ 2018. Extracted March 2019. Analysis performed by the Office of Surveillance and Epidemiology.



Conclusions:

- Prescribed mainly by primary care providers
- Estimated 2.3 to 2.5 million pediatric patients annually received montelukast prescription
- Mostly prescribed for asthma, followed by allergic rhinitis and cough
- Significant off-label use for cough


Observational Literature
Postmarketing Reports (FAERS)
Sentinel Distributed Database
FDA Review
Clinical Trial Safety Data
Pediatric Utilization Data
Nonclinical Data

Postmarketing Reports

The FDA Adverse Event Reporting System (FAERS)

- Searchable database of adverse event, medication error report, and product quality complaints submitted to FDA.
  - Voluntary communication from an individual (e.g., healthcare professional, consumer) describing one or more suspected adverse events
  - From 1969-2019, 18 million reports received for all drugs
- Supports the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products.

Postmarketing Reports

Strengths

- Detection of events not seen in clinical trials (“signal generation”)
- Detection of events with rare background rate
- Identification of possible risk factors, populations, and other clinically significant emerging safety concerns
- Conduit for the general public to directly communicate safety concerns to the FDA in terms of specific patient experiences

Limitations

- Causal relationship between a product and event is not required
- Reports do not always contain enough detail to properly evaluate an event
- FDA does not receive voluntary reports for every adverse event or medication error that occurs with a product
- Many factors can influence whether or not an event will be reported
- Cannot be used to calculate the incidence of an adverse event or medication error

Postmarketing Reports for Suicide

Results from FAERS

- Received from February 20, 1998*, to May 31, 2019
- 82 unique cases of completed suicide
- Majority of cases (48/82, 59%) did not contain sufficient information for appropriate evaluation of the relationship between montelukast and the adverse events
- Missing documentation in many cases
- Remaining well-documented cases contained medications or comorbidities that may increase the risk of self-harm

*Date of U.S. drug approval

Postmarketing Reports for Other NP Events

Previous Postmarketing Reviews Related to NP Events

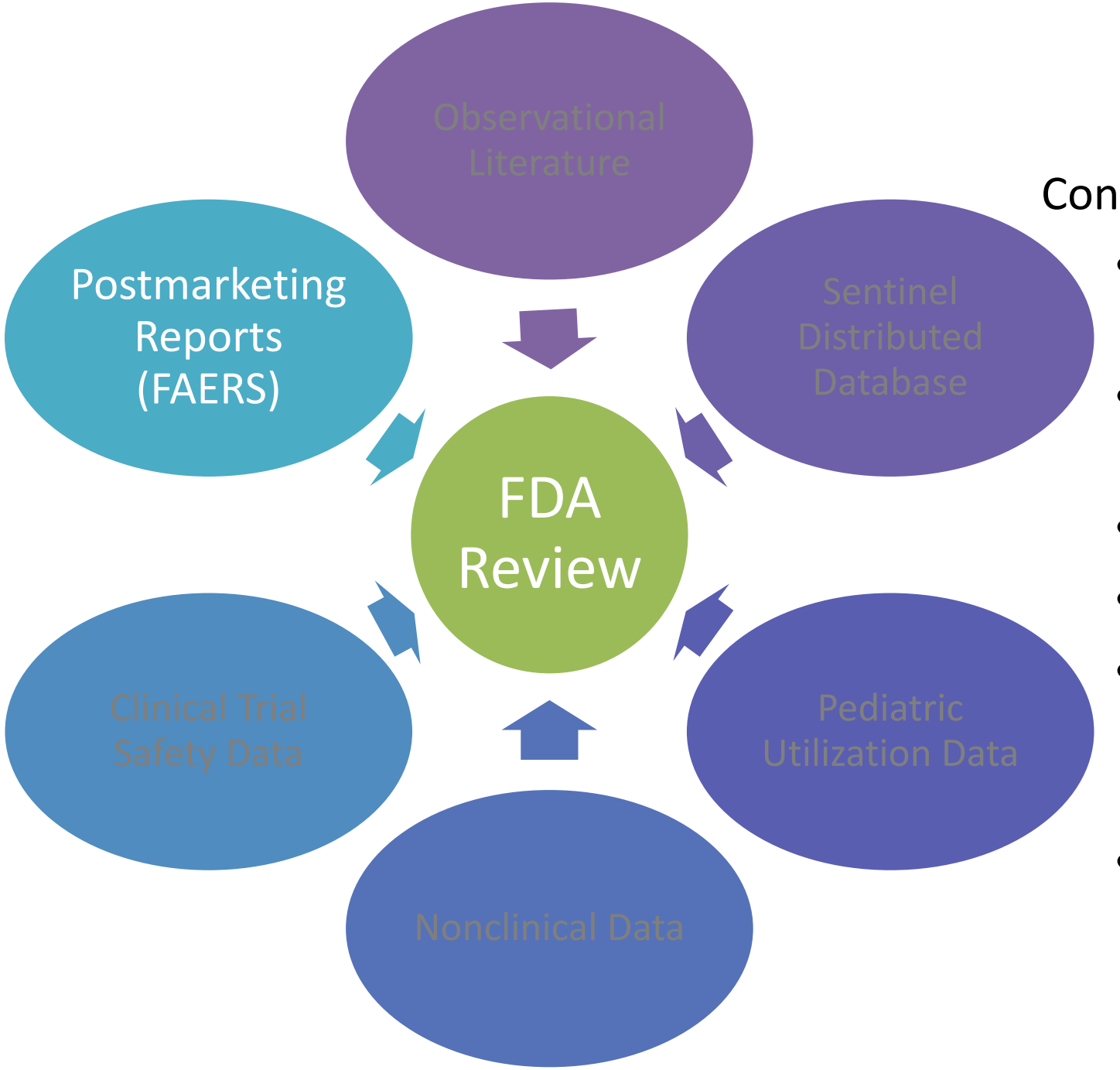
- 12/19/08 - Mood, Cognitive, Perception, Sleep and Movement Adverse Events
  - Neuropsychiatric events added to label
- 06/30/10 - Disorientation
  - Disorientation added to label
- 05/14/11 - Vocal and Motor Tics, Seizures and Brain Damage, Status Epilepticus, Death
- 02/21/14 - Suicide, Suicidal Ideation, Depression, Agitation, Anxiety, Aggressive Behavior, Hallucinations, Disorientation
- 09/02/14 - Aggression, Anxiety, Depression, Hallucination, Sleep Disorder, Suicidal Behavior
- 12/29/17 - Excoriation, Hyperkinesia, Obsessive Compulsive Disorder, Events after Withdrawal
  - Obsessive compulsive symptoms added to label
- 06/07/19 - Dysphemia, Stuttering
  - Dysphemia added to label

*Date of U.S. drug approval

Postmarketing Reports for Other NP Events

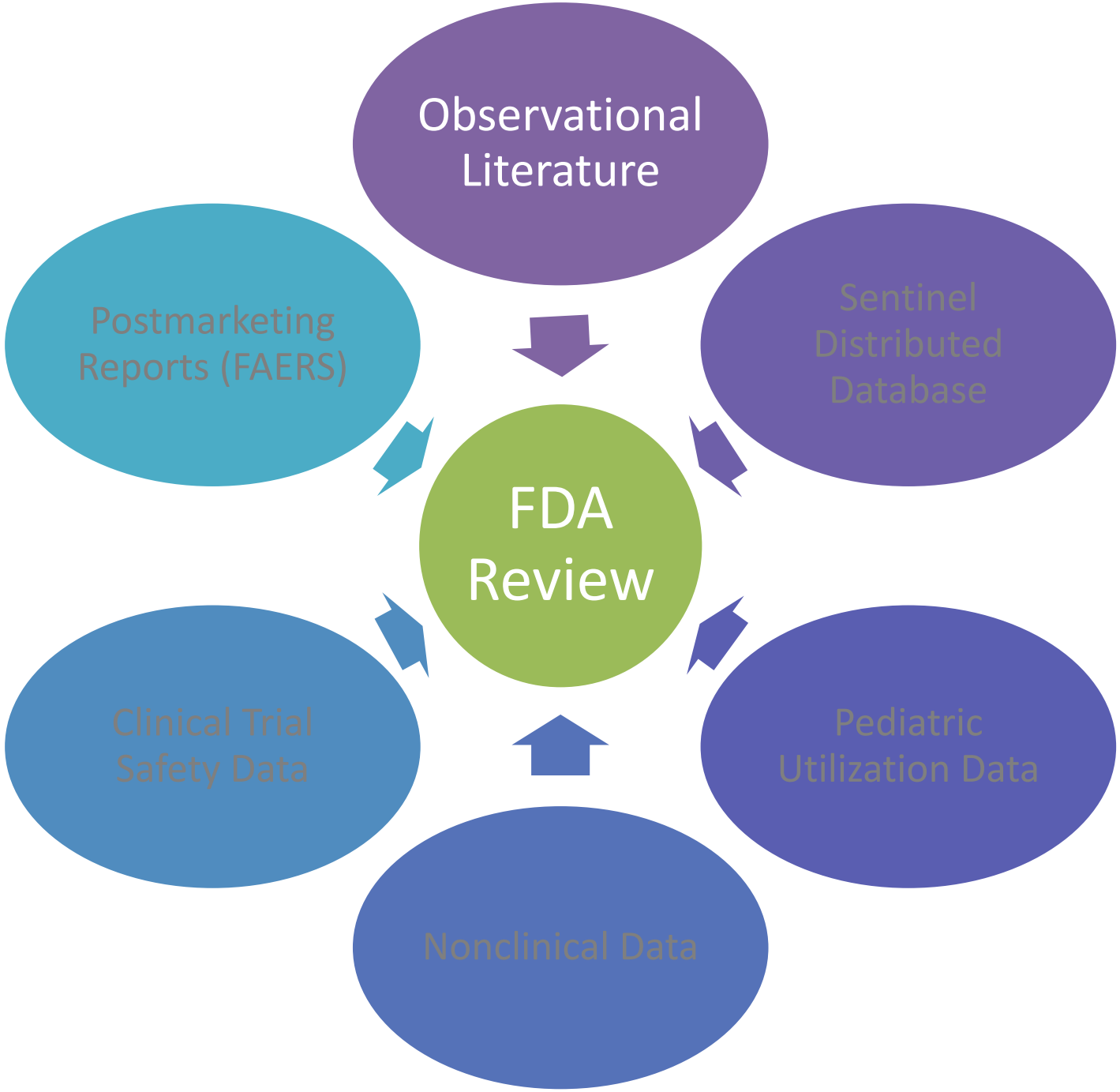
Additional Features:

- Wide spectrum of types of events
- Range in severity
- Variable time to onset
- No clear risk factors identified (other than pre-existing NP disorders)
- Limited reports about withdrawal symptoms or tapering dose
- Frequent mention of lack of awareness of NP events



Conclusions:

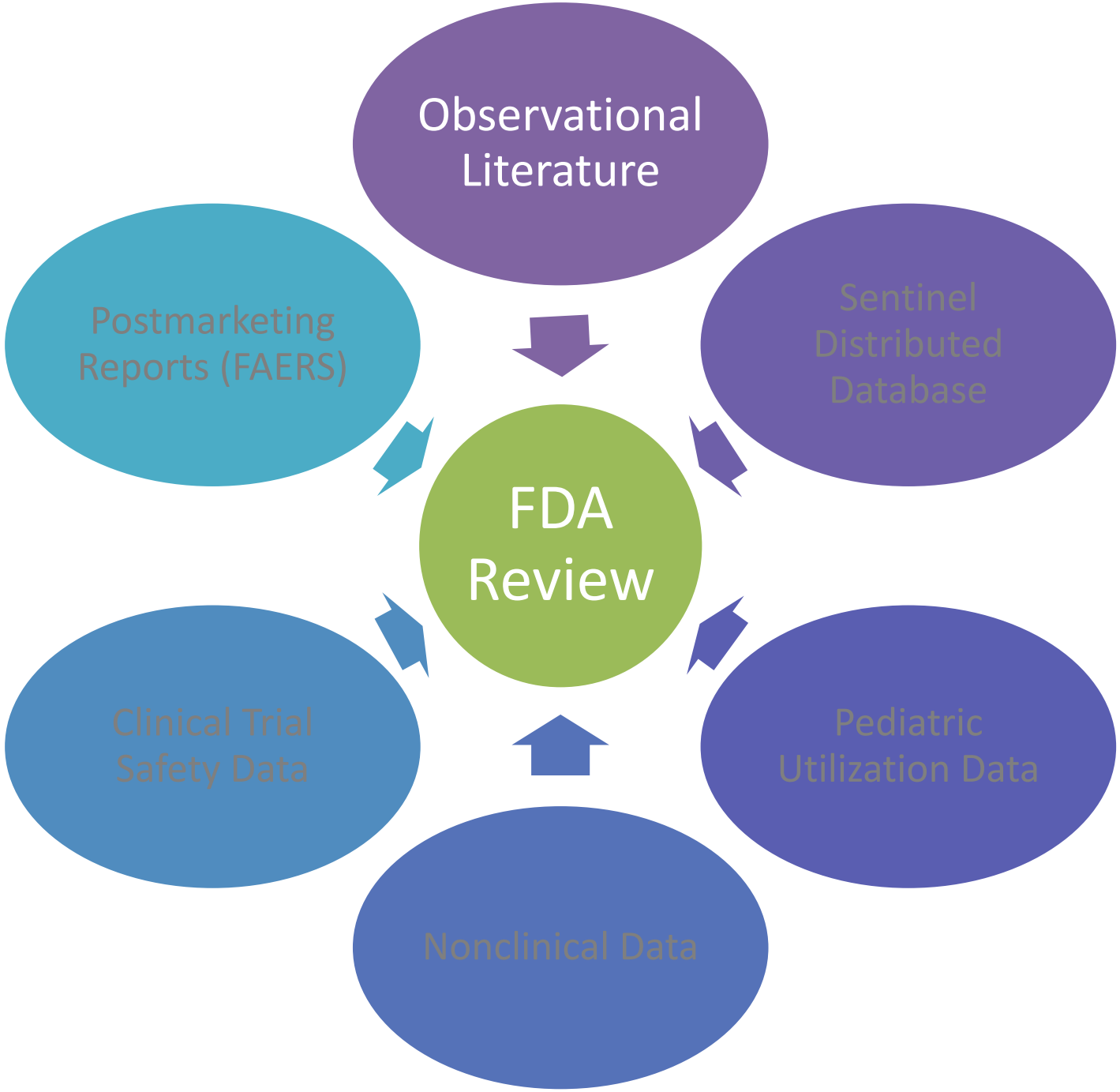
- Primary source of NP safety signal
- Wide range of symptoms and severity reported
- Variable time to onset
- No clear risk factors identified
- Confounding factors and limited information make it difficult to show causality
- Unable to determine frequency


Observational Literature
Postmarketing Reports (FAERS)
Sentinel Distributed Database
FDA Review
Clinical Trial Safety Data
Pediatric Utilization Data
Nonclinical Data

Literature Review

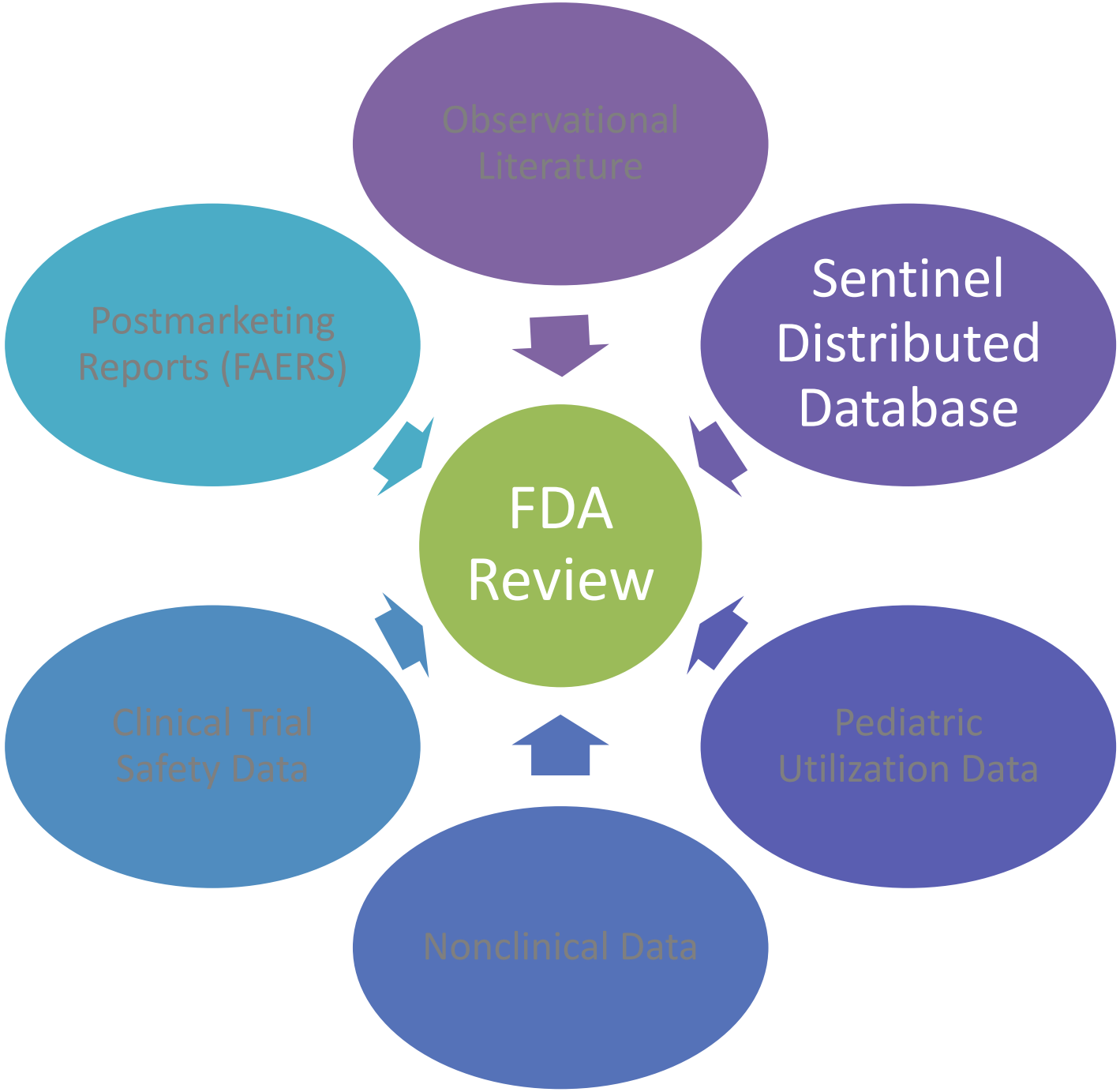
Four studies provided analysis relevant to montelukast use and neuropsychiatric outcomes:

1. Risk of suicide attempt in asthmatic children and young adults prescribed leukotriene-modifying agents: a nested case-control study showed a null association; Schumock et al. (2012)
2. Asthma and self-harm: a population-based cohort study in Taiwan showed no relationship; Chen et al. (2014)
3. Exploring the possible association between Montelukast and neuropsychiatric events among children with asthma: a matched nested case-control study showed a null association; Ali et al. (2015)
4. Neuropsychiatric adverse drug reactions in children initiated on montelukast in real-life practice showed a > 9-fold increased risk of NP events with montelukast use; Bénard et al. (2017)



Conclusions:

- Mixed results from observational studies


Observational Literature
Postmarketing Reports (FAERS)
Sentinel Distributed Database
FDA Review
Clinical Trial Safety Data
Pediatric Utilization Data
Nonclinical Data

Sentinel Distributed Database

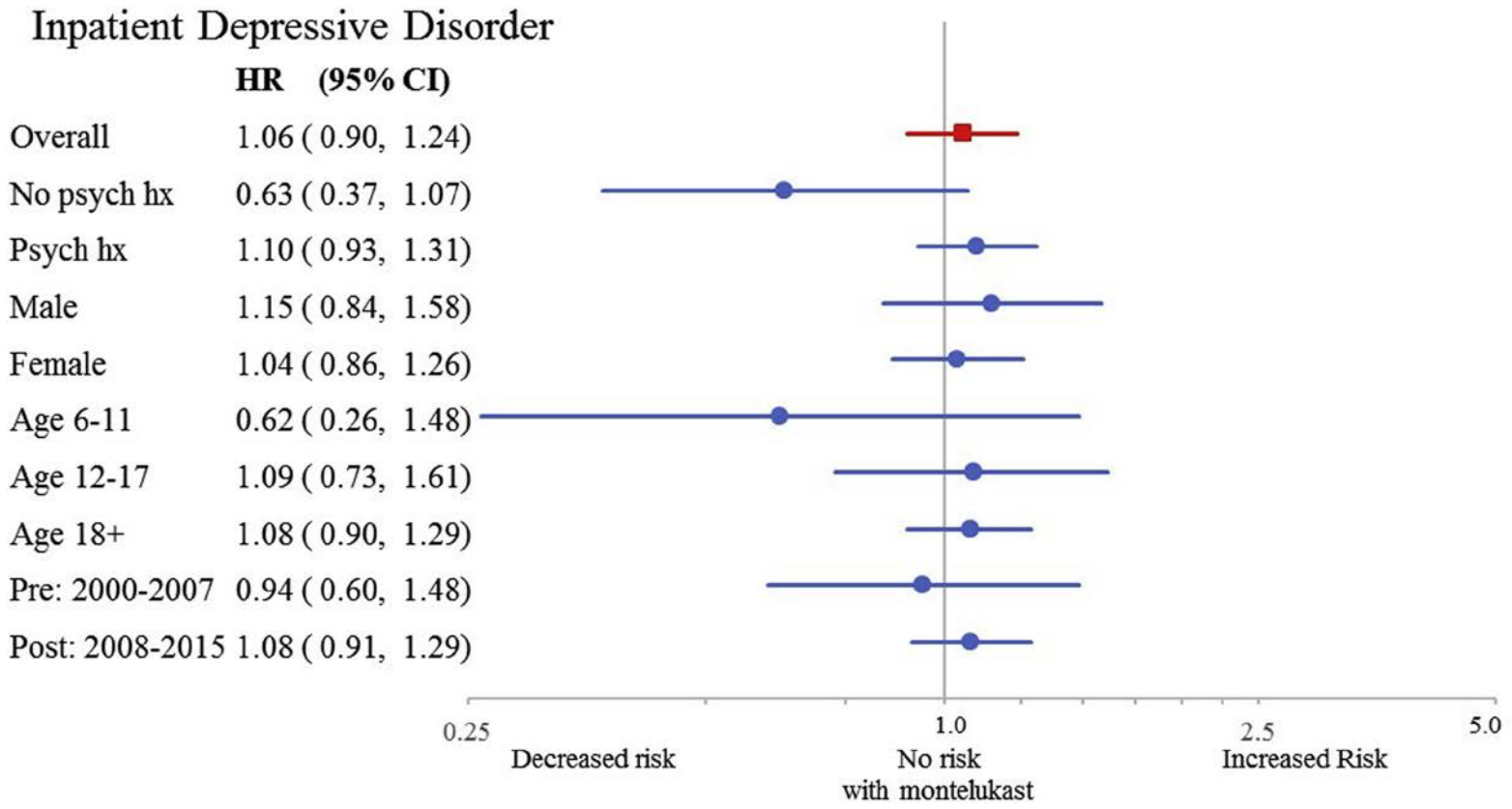
- Data Source: Sentinel Distributed Database (SDD)
  - Uses data partner sites that are large national insurers and integrated delivery care networks
  - Medical and pharmacy data, including inpatient and outpatient diagnoses and procedures, and prescription records
  - Based on claims data not full medical records or electronic health records

SDD Study - Design

- Exposure:
  - Incident montelukast or ICS between January 1, 2000 to September 30, 2015
- Outcomes:
  - Inpatient depressive disorder
  - Outpatient depressive disorder
  - Hospitalization due to self-harm
  - Death by completed suicide

SDD Study - Results

No statistical association was observed between montelukast and inpatient depressive disorder



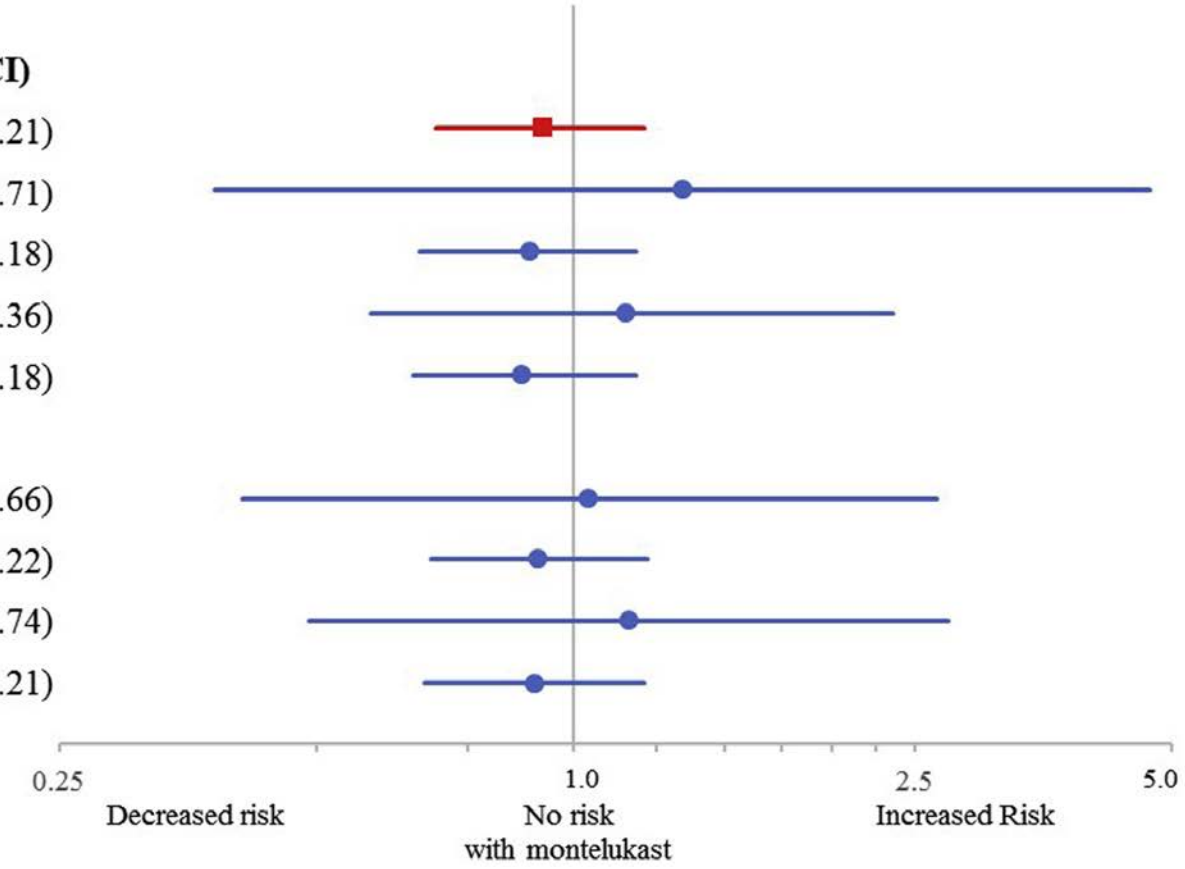
Sansing-Foster V, Haug N, Mosholder A, Cocoros NM, Bradley M, Ma Y, Pennap D, Dee EC, Toh S, Pestine E, Petrone AB, Kim I, Lyons JG, Eworuke E. Risk of Psychiatric Adverse Events Among Montelukast Users. J Allergy Clin Immunol Pract. 2021 Jan;9(1):385-393.e12.

SDD Study - Results

No statistical association was observed between montelukast and self-harm

Self-Harm

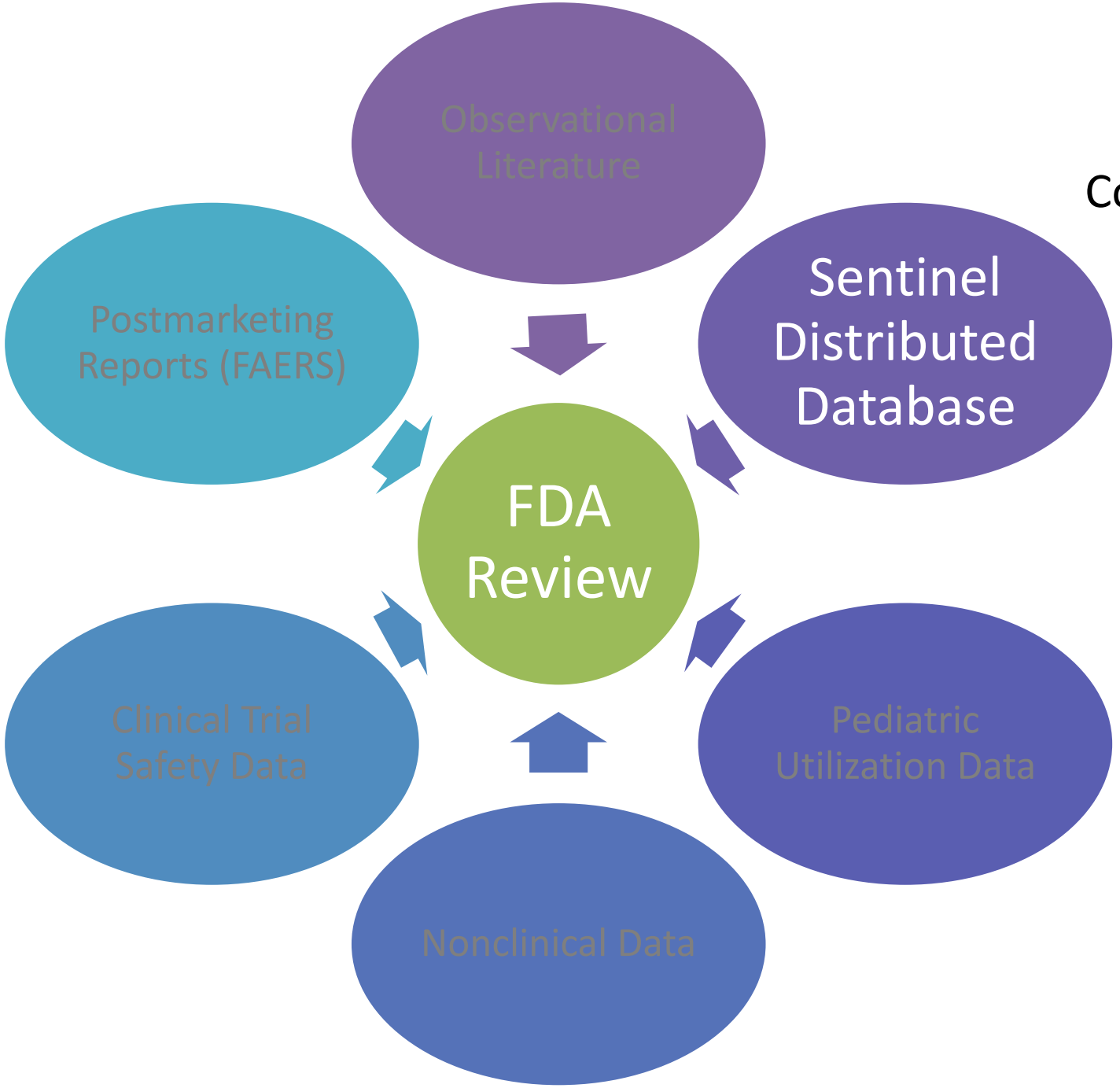
	HR (95% CI)
Overall	0.92 (0.69, 1.21)
No psych hx	1.34 (0.38, 4.71)
Psych hx	0.89 (0.66, 1.18)
Male	1.16 (0.58, 2.36)
Female	0.87 (0.65, 1.18)
Age 6-11	- -
Age 12-17	1.04 (0.41, 2.66)
Age 18+	0.91 (0.68, 1.22)
Pre: 2000-2007	1.16 (0.49, 2.74)
Post: 2008-2015	0.90 (0.67, 1.21)



Sansing-Foster V, Haug N, Mosholder A, Cocoros NM, Bradley M, Ma Y, Pennap D, Dee EC, Toh S, Pestine E, Petrone AB, Kim I, Lyons JG, Eworuke E. Risk of Psychiatric Adverse Events Among Montelukast Users. J Allergy Clin Immunol Pract. 2021 Jan;9(1):385-393.e12.

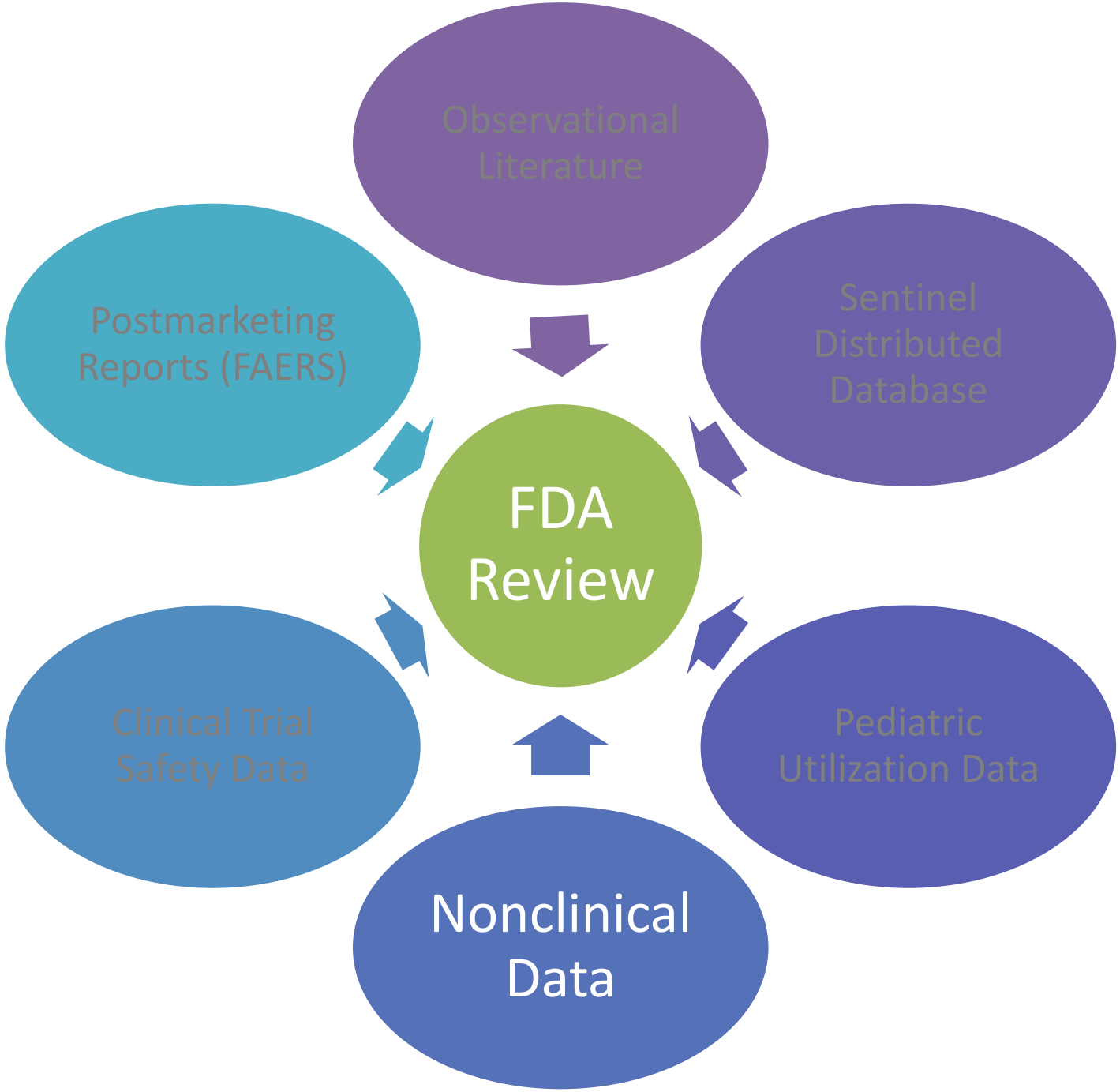
SDD Study - Limitations

- ICS has poorer adherence relative to montelukast
- Did not adjust for socioeconomic status
- Non-proportional hazards for study outcomes
- Channeling bias due to communications and labeling changes
- Underpowered to rule out an increased risk of 24% (upper bound of CI)



Conclusions:

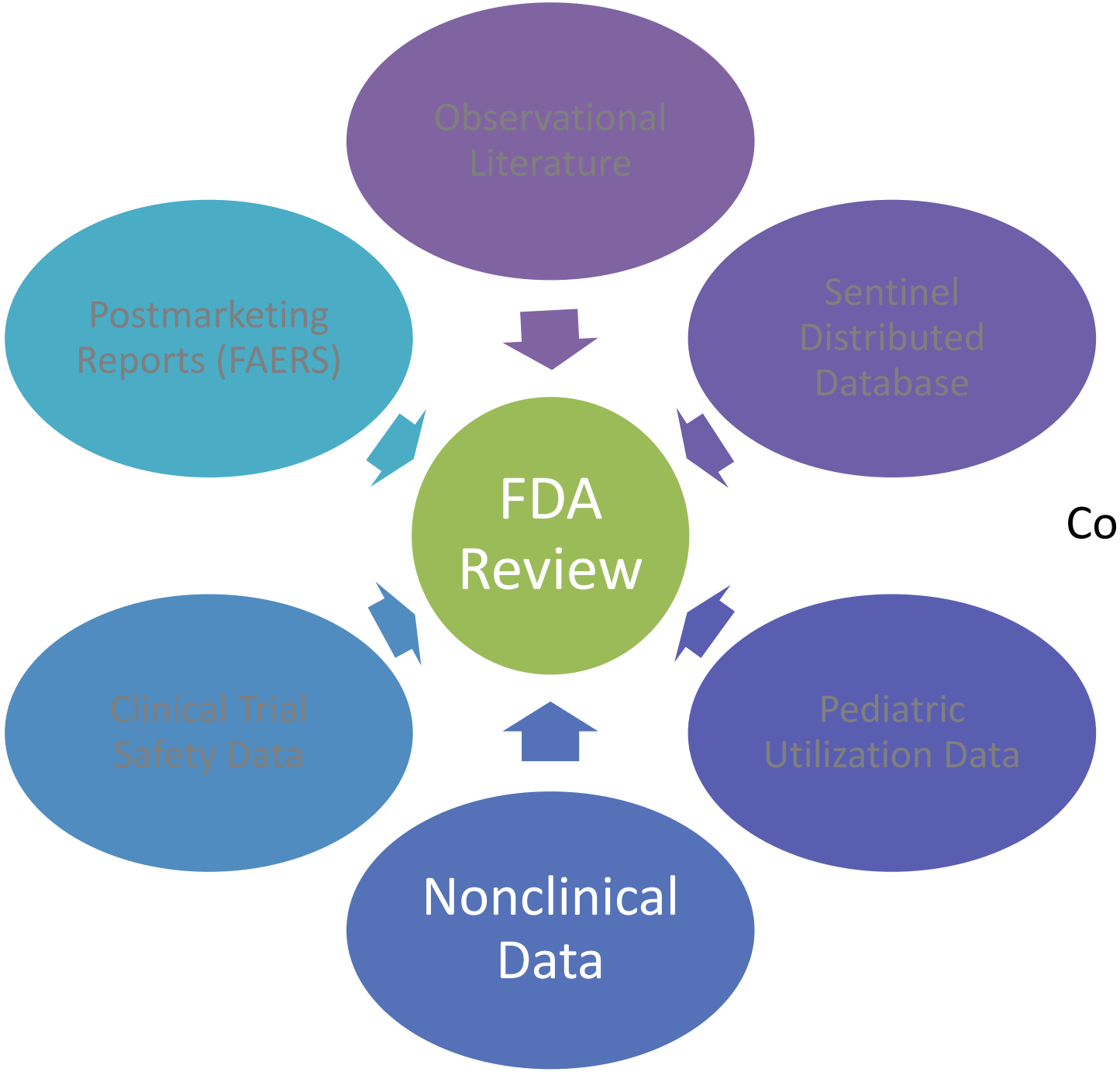
- No association between montelukast use and hospitalizations for depression or self-harm
- Most events occurred in patients with past psychiatric history
- Must consider study limitations in interpreting the findings


Observational Literature
Sentinel Distributed Database
Pediatric Utilization Data
Nonclinical Data
Clinical Trial Safety Data
Postmarketing Reports (FAERS)
FDA Review

Nonclinical Findings

- Original studies performed by the Sponsor showed montelukast can cross the blood-brain barrier in rats, but at low levels compared to other tissues*
- CysLT1 receptor expression in the human brain is very low
- Hypothesized mechanisms by which montelukast could gain access to the CNS have been difficult to reproduce

*At the time of the initial NDA review, brain exposure was felt to be relatively low compared to other tissues and thus the original product labeling notes minimal crossing of the blood brain barrier. FDA Pharmacology Review of Montelukast. NDA 20829 (1998).



Conclusions:

- Crosses BBB, relatively low brain exposure in rats
- Absence of CysLT-1 in brain; other potential mechanisms may exist
- Lack of clear mechanism for NP events

Advisory Committee Meeting

FDA convenes committees and panels to obtain independent expert advice on scientific, technical, and policy matters.

Pediatric Advisory Committee

Pediatricians

Allergists/Pulmonologists

Pediatric Research

Biomedical Ethics

Pediatric Psychiatrists

Patient-family representative

Drug Safety and Risk Management Advisory Committee

Risk communication

Risk management

Drug safety

Medical, behavioral, and biological sciences

Drug Abuse

Joint Committee Meeting

Advisory Committee Deliberations

- **Long-standing history of NP events**
- **Lack of strong safety signal in clinical trials**
- **Utilization Data**
  - Montelukast is primarily utilized in the outpatient retail setting
  - Prescribed mainly by general practice
  - Estimated 2.3 to 2.5 million pediatric patients annually received montelukast prescription
  - Mostly prescribed for asthma, followed by allergic rhinitis and cough
  - Significant off-label use for cough
- **FAERS postmarketing reports**
  - Primary source of NP safety signal
  - Wide range of symptoms and severity reported
  - Variable time to onset
  - No clear risk factors identified
  - Confounding factors and limited information make it difficult to show causality
  - Unable to determine frequency
- **Literature review**
  - Mixed results from observational studies
- **Sentinel study**
  - No association between montelukast use and hospitalizations for depression or self-harm
  - Most events occurred in patients with past psychiatric history
  - Must consider study limitations in interpreting the findings
- **Nonclinical data**
  - Crosses BBB, relatively low brain exposure in rats
  - Absence of CysLT-1 in brain; other potential mechanisms may exist
  - Lack of clear mechanism for NP events
- **Communication is a challenge**
  - Existing safety issue
  - Available data have limitations and/or inconclusive

Advisory Committee Public Response

Public

- 15 speakers in the open public hearing
- 232 comments posted to the docket
- Main Themes included:
  - Strong sentiment to issue a Boxed Warning
  - Lack of awareness of potential risk
  - Unfavorable risk/benefit for Allergic Rhinitis

Advisory Committee Questions

1) Discuss the neuropsychiatric safety findings presented for montelukast
2) Discuss the current labeling for montelukast, including:
   - Current Warnings and Precautions
   - Request for Medication Guide and Boxed Warning
3) Discuss your recommendations for communication strategies
   - Target audience
   - Target organizations
   - Modalities of communication

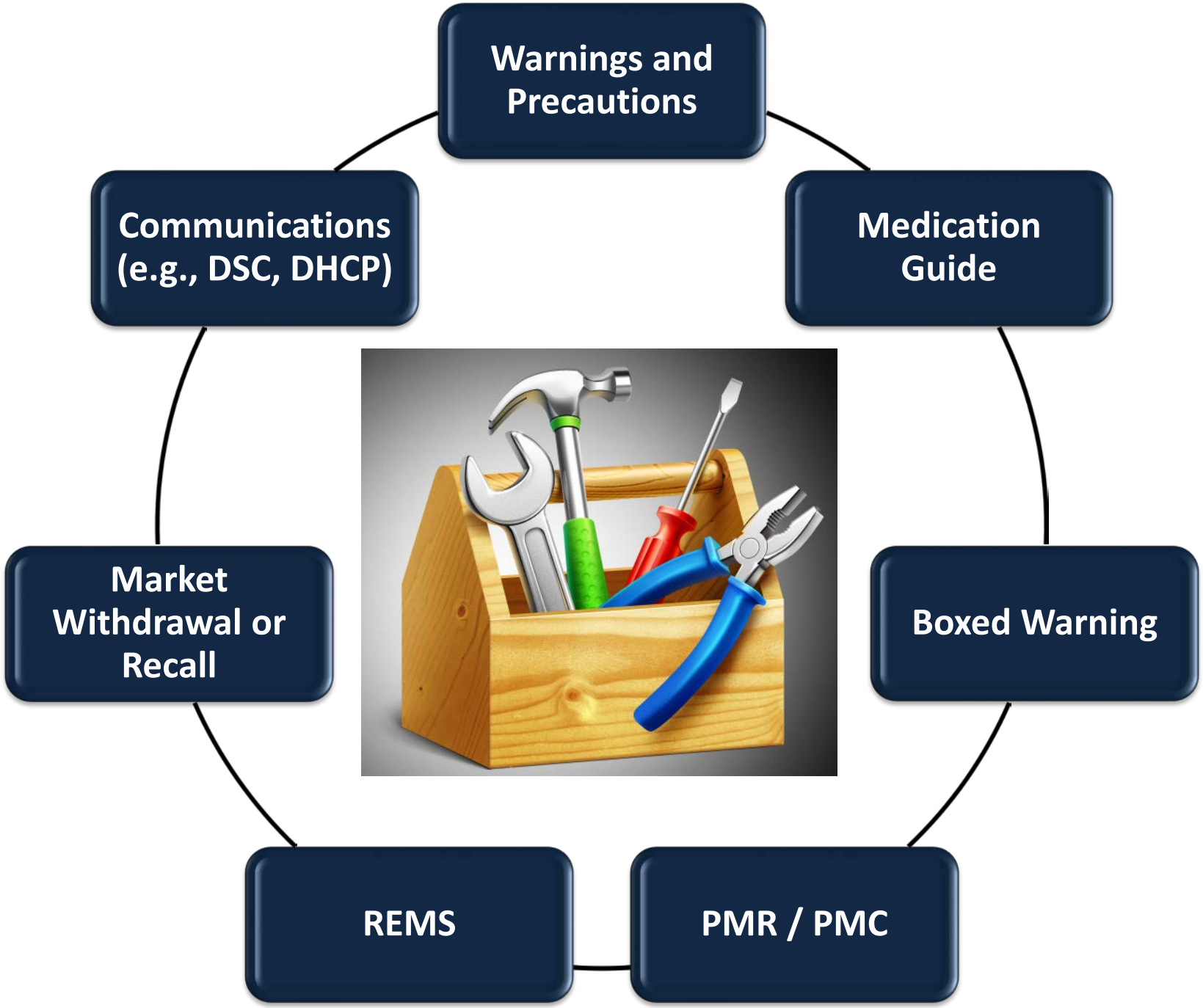
Advisory Committee Outcome

Panel Members

- No voting questions
- Main Themes included:
  - Data inconclusive
  - Disconnect between data and public comments
  - Need for more research/better data
  - Mixed opinions on Boxed Warning
  - Risk/benefit needs to be re-evaluated
  - Continued lack of awareness even among health care professionals

Outline

- Product Information
- Neuropsychiatric Events and Safety Labeling
- Regulatory History Related to Neuropsychiatric Findings
- **Regulatory Considerations**
- Decision Making
- Updated Safety Labeling
- Discussion Topics
- Challenge Questions


Warnings and Precautions
Medication Guide
Boxed Warning
PMR / PMC
REMS
Market Withdrawal or Recall
Communications (e.g., DSC, DHCP)

Warnings and Precautions

Communications (e.g., DSC, DHCP)

Medication Guide

Removal or correction of a distributed product



Market Withdrawal or Recall

Boxed Warning

Drug safety program that FDA can require for certain medications with serious safety concerns

REMS

PMR / PMC

Studies and clinical trials that sponsors conduct after approval to gather additional information about a product's safety, efficacy, or optimal use

Warnings and Precautions

Medication Guide

Boxed Warning

PMR / PMC

Studies and clinical trials that sponsors conduct after approval to gather additional information about a product's safety, efficacy, or optimal use

REMS

Drug safety program that FDA can require for certain medications with serious safety concerns

Market Withdrawal or Recall

Removal or correction of a distributed product

Communications (e.g., DSC, DHCP)



Boxed Warning

- Used to call attention to serious or life-threatening risks
- 21 CFR 201.57(c)(1)
  - *Adverse reaction so serious in proportion to benefit that it is essential to consider in assessing risks and benefits of using the drug*
  - *Serious adverse reaction that can be prevented or reduced by appropriate use*
  - *Approved with restrictions to ensure safe use because drug can be safely used only if distribution or use is restricted*

Labeling - Warnings and Precautions

- Product labeling conveys essential information for safe and effective use
- Neuropsychiatric Events were listed in the Warnings and Precautions section (5.4) since 2007

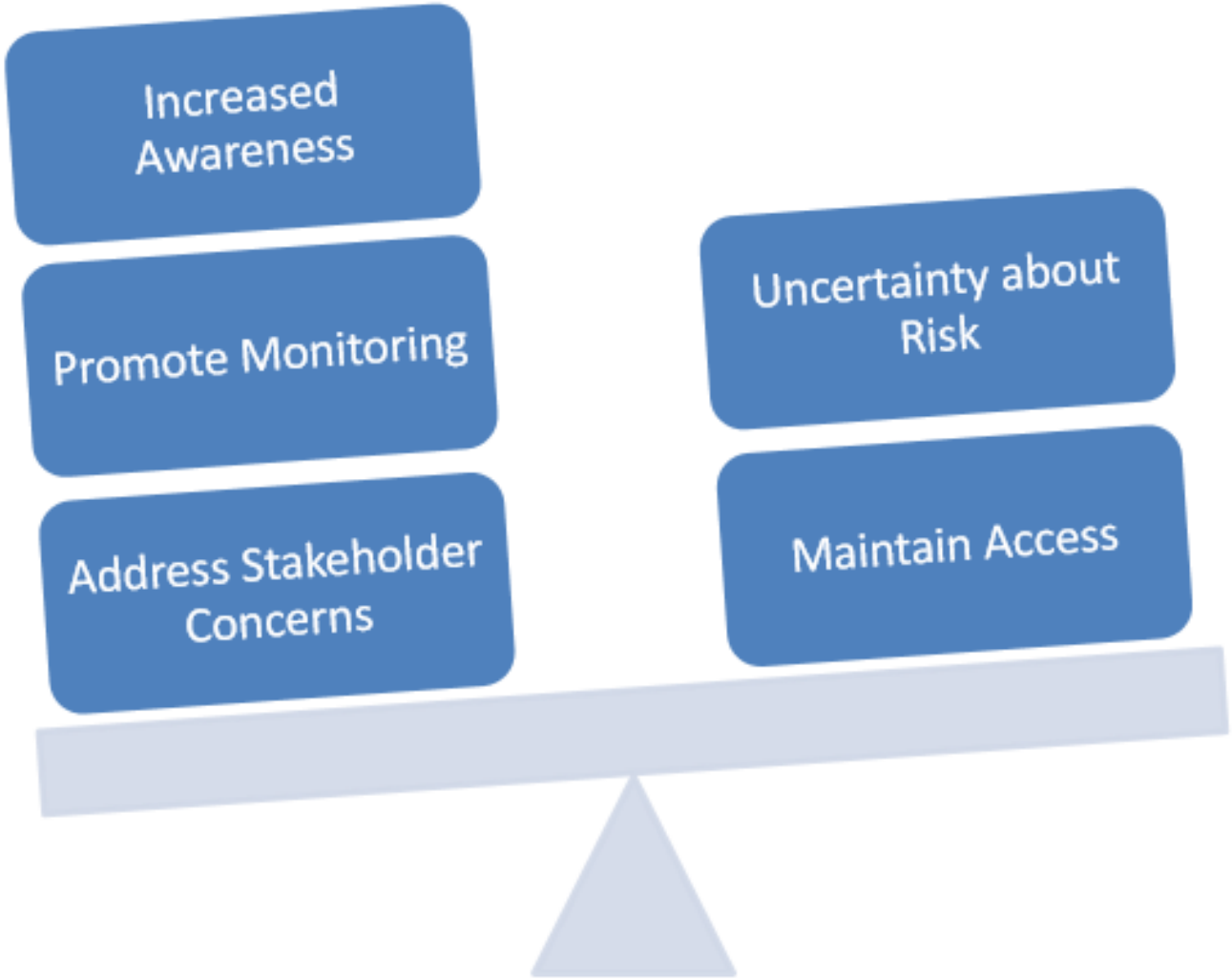
Medication Guide

- Since 1998, Medication Guides or MedGuides have been required for a limited number of medications that "pose a serious and significant public health concern" - 21 CFR 208
- MedGuides are required if FDA determines one or more of the following exist:
  - Patient Labeling could help prevent serious adverse events
  - Serious risks that could affect the patient's decision to use the product
  - Adherence to directions is crucial to effectiveness of the product
- Distribution Requirements
  - Manufacturers must provide sufficient numbers of MedGuides or means for the dispenser to produce
  - MedGuide must be dispensed along with the product
- Currently more than 400 drugs have MedGuides
  - Complete list: http://www.fda.gov/Drugs/DrugSafety/ucm085729.htm

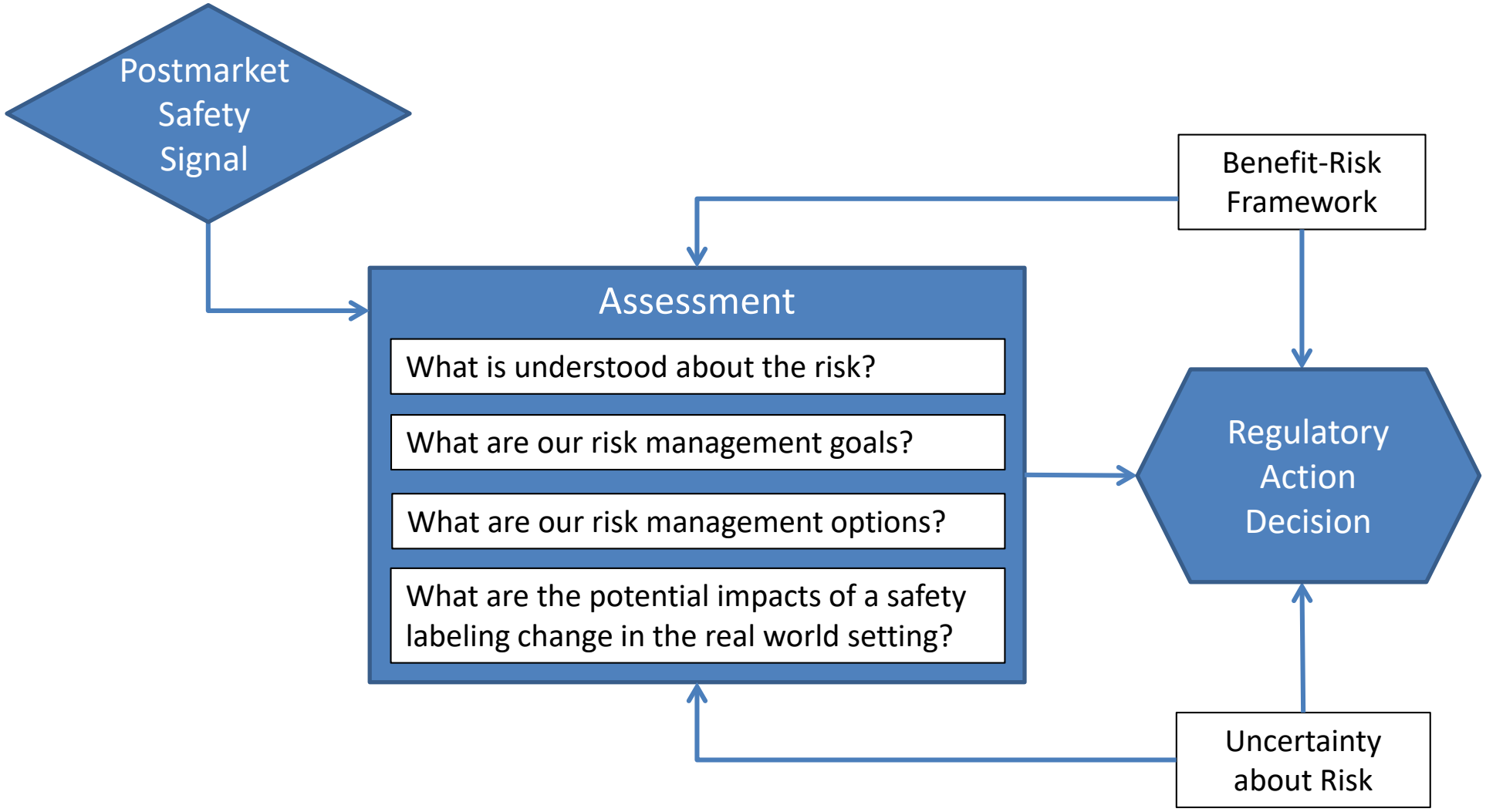
Outline

- Product Information
- Neuropsychiatric Events and Safety Labeling
- Regulatory History Related to Neuropsychiatric Findings
- Regulatory Considerations
- **Decision Making**
- Updated Safety Labeling
- Discussion Topics
- Challenge Questions

Internal Discussions: Key Considerations



Decision Framework for Safety Labeling Changes



Setting context – Current perspectives on Benefit-Risk

Allergic Rhinitis (AR)

Dimension	Conclusions and Reasons
Analysis of Condition	• AR is a chronic, symptomatic condition affecting 60 million Americans • Reduces quality of life, sometimes drastically, but is not life-shortening • Early immunotherapy (e.g., allergy shots) may stop the progression to asthma
Current Treatment Options	• First-line therapies are available over the counter for short- and long-term use • Subcutaneous and sublingual immunotherapy highly effective, alters course of disease, and relatively safe • Some patients symptomatic despite available treatments
Benefit	• Modest benefit in total nasal symptom score in clinical trials • No more effective than oral histamines and nasal steroids • Oral administration • Treats comorbid asthma
Risk	• Good safety profile, except NP events

Asthma

Dimension	Conclusions and Reasons
Analysis of Condition	• Heterogeneous condition ranging from mild to severe disease • Severe asthma associated with significant morbidity and in rare cases, mortality • Very common - 25 million Americans are affected by mild to moderate asthma, and it is the leading chronic disease in children
Current Treatment Options	• Beta agonists (short- and long-acting) and inhaled steroids (ICS) are first-line therapies • Potentially two populations with unmet need: (1) those suffering the most severe cases of asthma and (2) possibly those requiring an oral therapy option
Benefit	• Some populations may respond especially well to this target; however, generally less effective than guideline recommended 1st line therapies • Oral administration
Risk	• Good safety profile, except NP events

What did we understand about the risk?

- Patients taking montelukast have experienced a wide variety of severe NP Adverse Events (AEs)
- Available evidence is limited to postmarketing spontaneous reports
  - AEs not seen in premarket trials
- A Sentinel study was equivocal (could neither support nor eliminate association)
- Evidence suggests history of NP events may be a risk factor
- Significant uncertainties remain
  - Cause/mechanism
  - Frequency
  - Timing– onset, duration, reversal upon discontinuation
- Drug also used off-label for acute respiratory and non-specified cough

What were our goals?

Product use goals

- Patients and providers are aware of the potential risk of NP AEs
- Patients and providers make informed benefit/risk decisions about use
- Decrease off-label use; “inappropriate” use
- Patients and providers monitor for NP events and take appropriate action if suspected
- Maintain access to patients who would benefit from the product/for whom benefit outweighs the risk

Other Agency goals

- Ensure FDA’s decision-making is supported by science
- Increase scientific understanding of the frequency, underlying cause, and risk factors
- Appropriately engage stakeholders; respond to stakeholders’ concerns

What were our options?

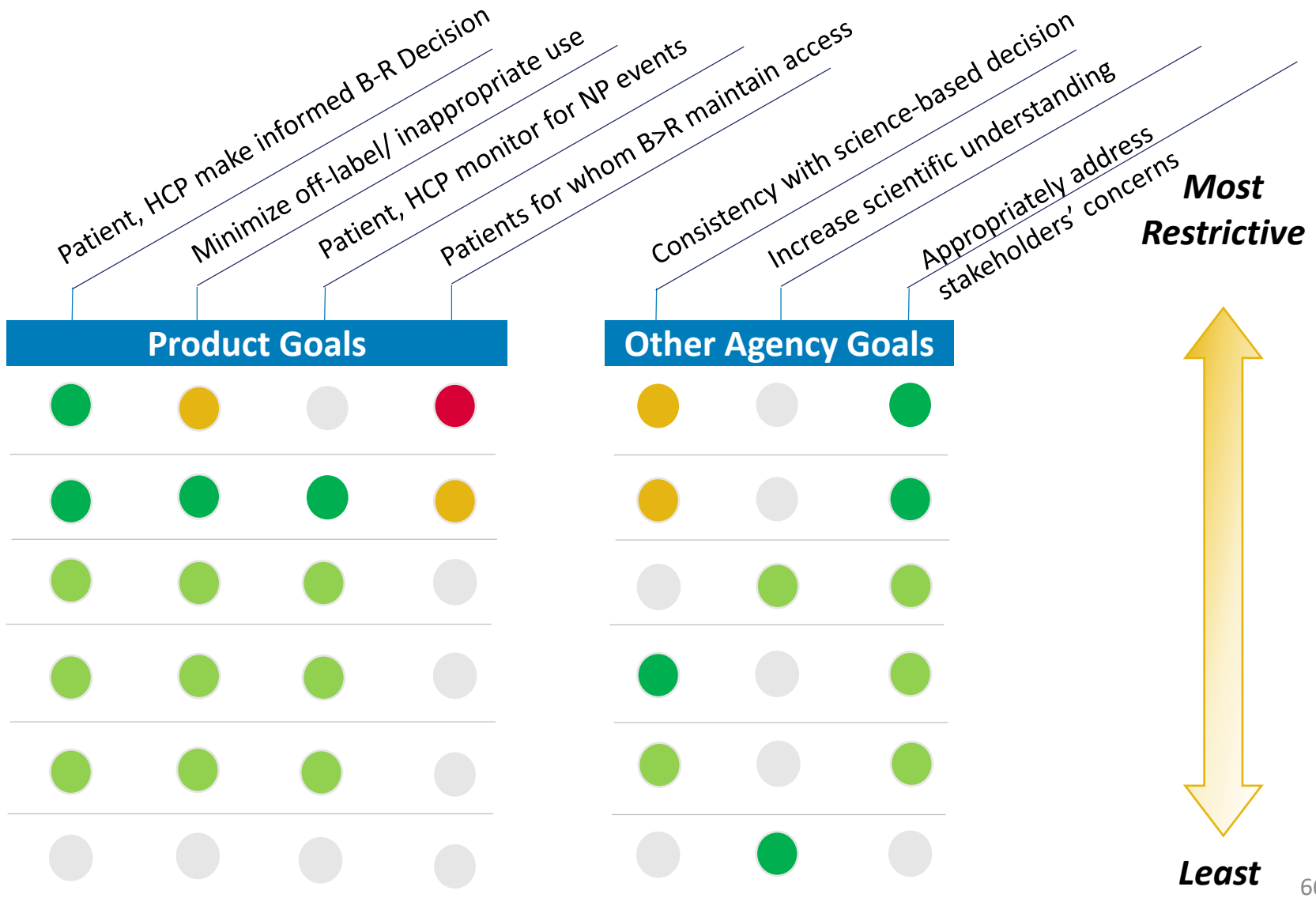
- Re-examine B-R assessment of montelukast for each indication
- REMS (maximize labeling first)
- Add Boxed Warning
- Encourage/support clinical guidelines development (public-private partnerships)
- Other Safety Labeling (e.g., Warnings and Precautions, MedGuide)
- Communications (e.g., Dear Health Care Provider Letter, Drug Safety Communications, Medscape)
- Conduct or require additional studies

How might options affect our goals?

- Expect outcomes that <u>support</u> the goal
- Outcome <u>potentially contrary</u> to goal
- Expect outcomes <u>contrary</u> to the goal

Options

1. Remove AR indication
2. Add boxed warning
3. Encourage/support guidelines
4. Communication (e.g., Letter, Medscape)
5. Labeling change(s) other than BW (e.g, Medguide)
6. Conduct/require add'l studies

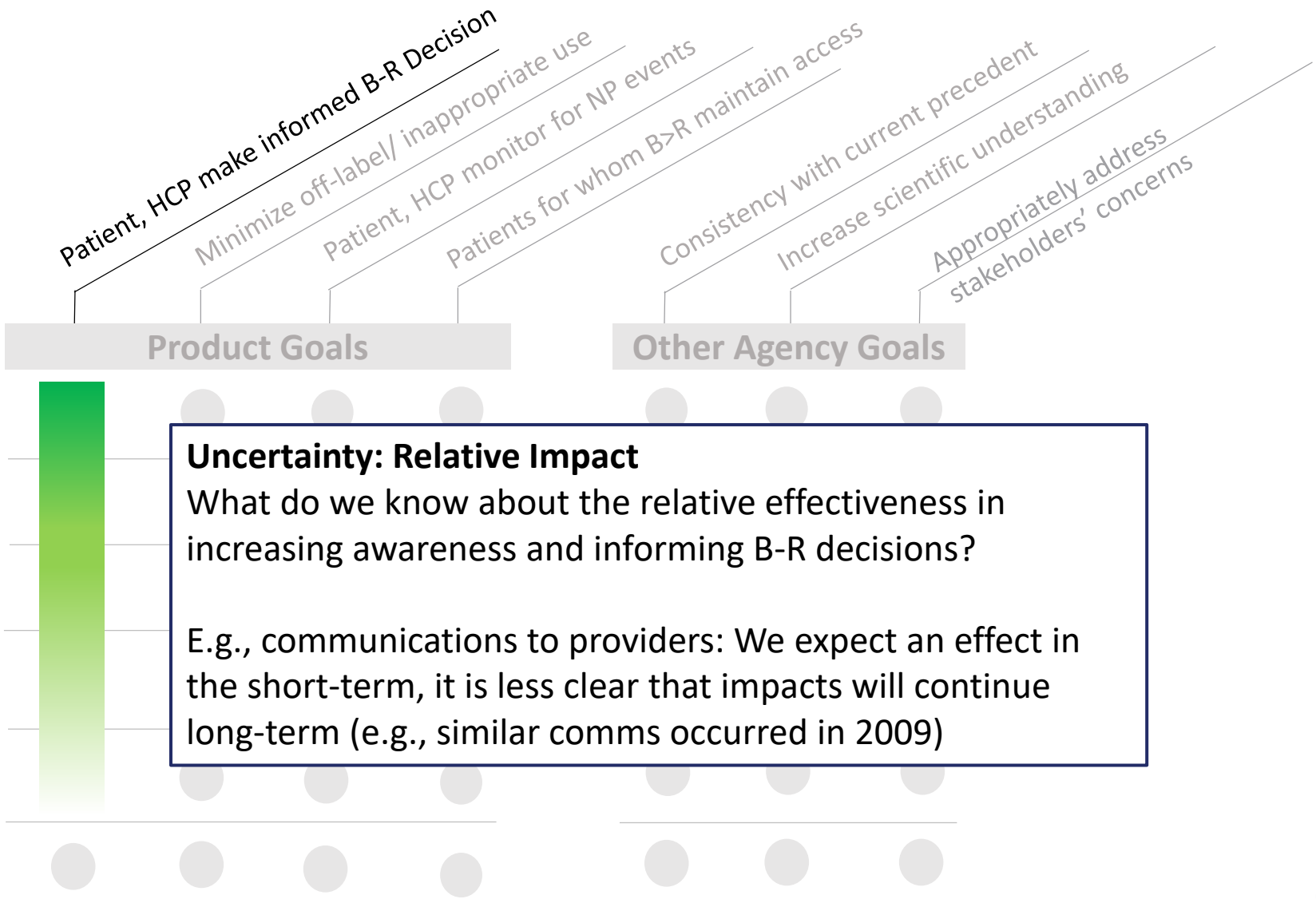


How might options affect our goals?

- Expect outcomes that support the goal
- Outcome potentially contrary to goal
- Expect outcomes contrary to the goal

Options

1. Remove AR indication
2. Add boxed warning
3. Encourage/support guidelines
4. Communication (e.g., DHCP, DSC, Medscape)
5. Labeling change(s) other than BW (e.g, WP, Medguide)
6. Conduct/require add'l studies



Uncertainty: Relative Impact
What do we know about the relative effectiveness in increasing awareness and informing B-R decisions?

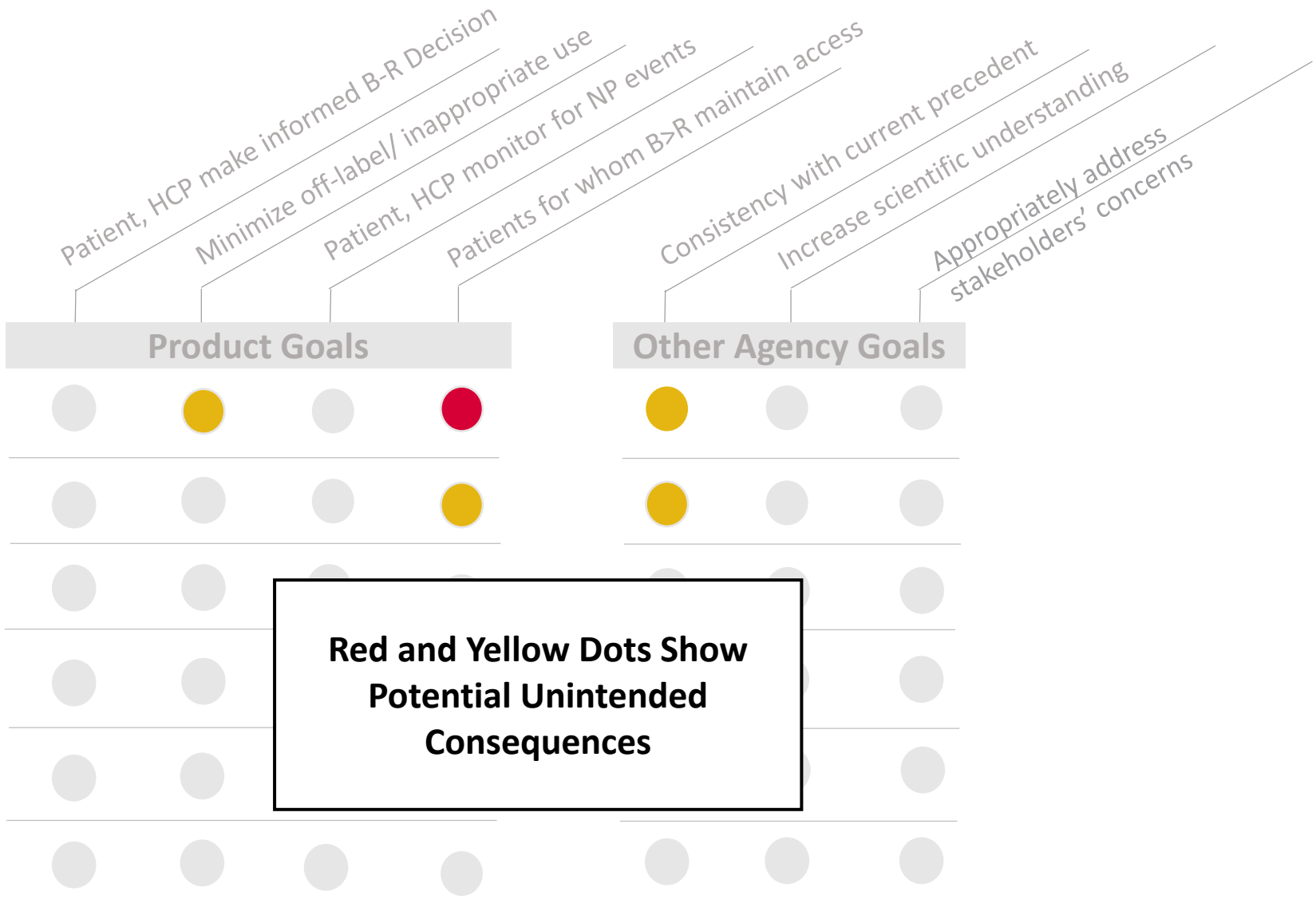
E.g., communications to providers: We expect an effect in the short-term, it is less clear that impacts will continue long-term (e.g., similar comms occurred in 2009)

How might options affect our goals?

- Expect outcomes that support the goal
- Outcome potentially contrary to goal
- Expect outcomes contrary to the goal

Options

1. Remove AR indication
2. Add boxed warning
3. Encourage/support guidelines
4. Communication (e.g., DHCP, DSC, Medscape)
5. Labeling change(s) other than BW (e.g, WP, Medguide)
6. Conduct/require add'l studies



Safety Labeling: Final Decisions

Boxed Warning

- Seriousness of the nature of the safety signal in proportion to the potential benefit (particularly for AR)
- Increase awareness among patients and providers about the risk of NP events
- Promote monitoring for these events
- Minimize off-label use

Indication for AR

- Treatment landscape and benefit-risk assessment of montelukast for AR had changed since its initial approval
  - Over-the-counter therapies available
  - Modest benefit in clinical trials
  - AR is typically a mild, symptomatic disease

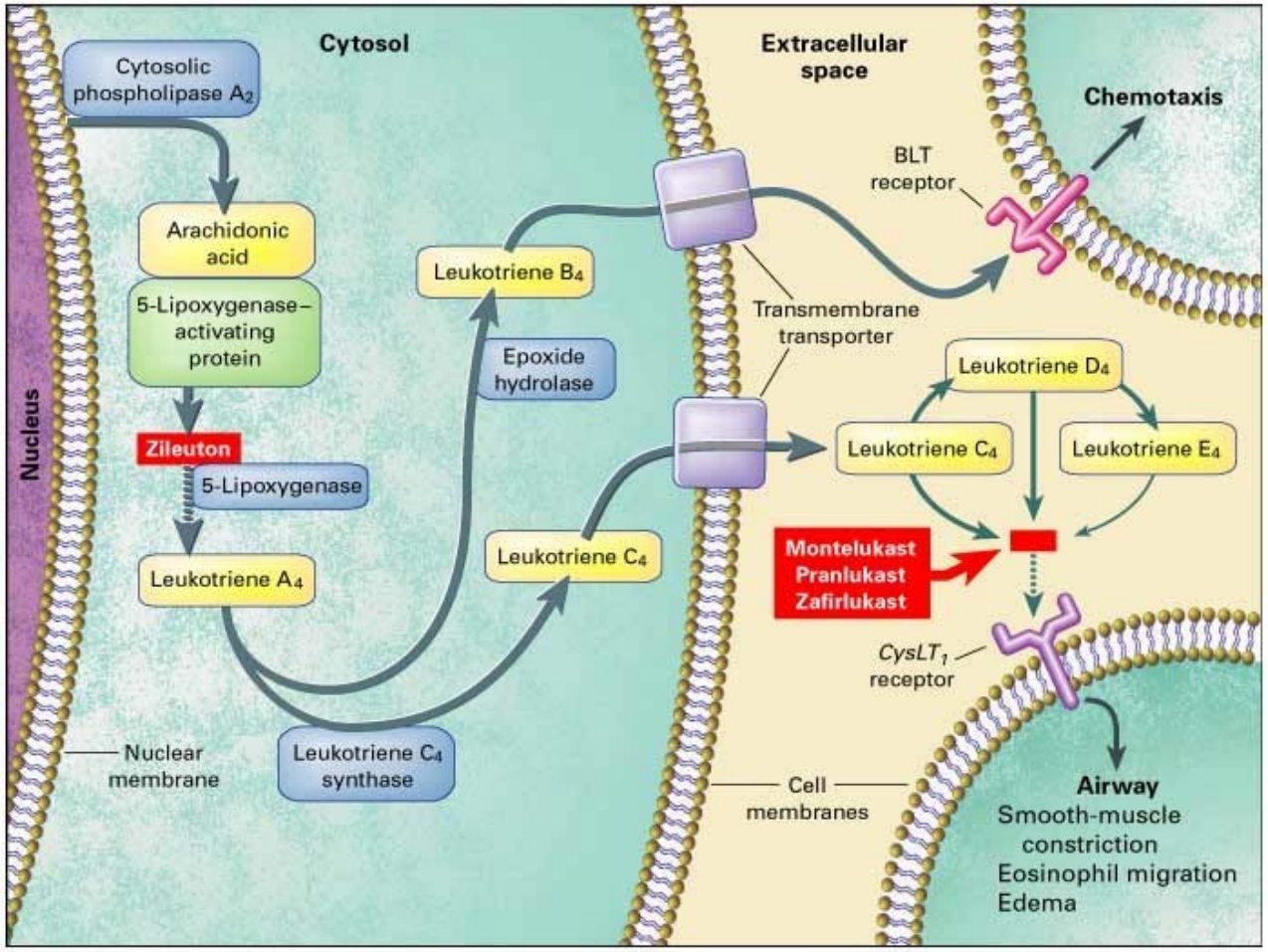
Indication for Asthma

- Unchanged
  - Variable severity of disease
  - Narrower spectrum of available therapies

Safety Labeling: Final Considerations

What about class labeling to add BW to other LTRAs?

- Neither are approved for AR, the indication for which the benefit-risk assessment has substantially changed.
- Few post-marketing reports of NP events with zafirlukast and zileuton.
- Montelukast is structurally dissimilar and does not share many chemical features with either zafirlukast or zileuton.



Drazen JM, Israel E, O'Byrne PM. Treatment of asthma with drugs modifying the leukotriene pathway. N Engl J Med. 1999;340(3):197-206.

Outline

- Product Information
- Neuropsychiatric Events and Safety Labeling
- Regulatory History Related to Neuropsychiatric Findings
- Regulatory Considerations
- Decision Making
- **Updated Safety Labeling**
- Discussion Topics
- Challenge Questions

Updated Safety Labeling Changes

- New Boxed warning
- Changed the indication for allergic rhinitis
- Expanded the Warnings and Precautions
- Created new Medication Guide

WARNING: SERIOUS NEUROPSYCHIATRIC EVENTS

See full prescribing information for complete boxed warning.

- **Serious neuropsychiatric events have been reported in patients taking (5.1).**
- **Discuss benefits and risks of with patients and caregivers (5.1).**
- **Monitor for neuropsychiatric symptoms in patients taking (5.1).**
- **Discontinue immediately if neuropsychiatric symptoms occur (5.1).**
- **Because the benefits of may not outweigh the potential risk of neuropsychiatric symptoms in patients with allergic rhinitis, reserve use for patients who have an inadequate response or intolerance to alternative therapies (1.3, 5.1).**

Safety Labeling Changes updated 4/2020

Montelukast Boxed Warning

WARNING: SERIOUS NEUROPSYCHIATRIC EVENTS

Serious neuropsychiatric (NP) events have been reported with the use of . The types of events reported were highly variable, and included, but were not limited to, agitation, aggression, depression, sleep disturbances, suicidal thoughts and behavior (including suicide). The mechanisms underlying NP events associated with use are currently not well understood *[see Warnings and Precautions (5.1)]*.

Because of the risk of NP events, the benefits of may not outweigh the risks in some patients, particularly when the symptoms of disease may be mild and adequately treated with alternative therapies. Reserve use of for patients with allergic rhinitis who have an inadequate response or intolerance to alternative therapies *[see Indications and Usage (1.3)]*. In patients with asthma or exercise-induced bronchoconstriction, consider the benefits and risks before prescribing .

Discuss the benefits and risks of with patients and caregivers when prescribing . Advise patients and/or caregivers to be alert for changes in behavior or new NP symptoms when taking . If changes in behavior are observed, or if new NP symptoms or suicidal thoughts and/or behavior occur, advise patients to discontinue and contact a healthcare provider immediately *[see Warnings and Precautions (5.1)]*.

Prescribing Information

Montelukast Package Insert

----------5 WARNINGS AND PRECAUTIONS----------

5.1 Neuropsychiatric Events

Serious neuropsychiatric (NP) events have been reported with use of montelukast. These postmarketing reports have been highly variable and included, but were not limited to, agitation, aggressive behavior or hostility, anxiousness, depression, disorientation, disturbance in attention, dream abnormalities, dysphemia (stuttering), hallucinations, insomnia, irritability, memory impairment, obsessive-compulsive symptoms, restlessness, somnambulism, suicidal thoughts and behavior (including suicide), tic, and tremor. NP events have been reported in adult, adolescent, and pediatric patients with and without a previous history of psychiatric disorder. NP events have been reported mostly during montelukast treatment, but some were reported after montelukast discontinuation…

Prescribing Information

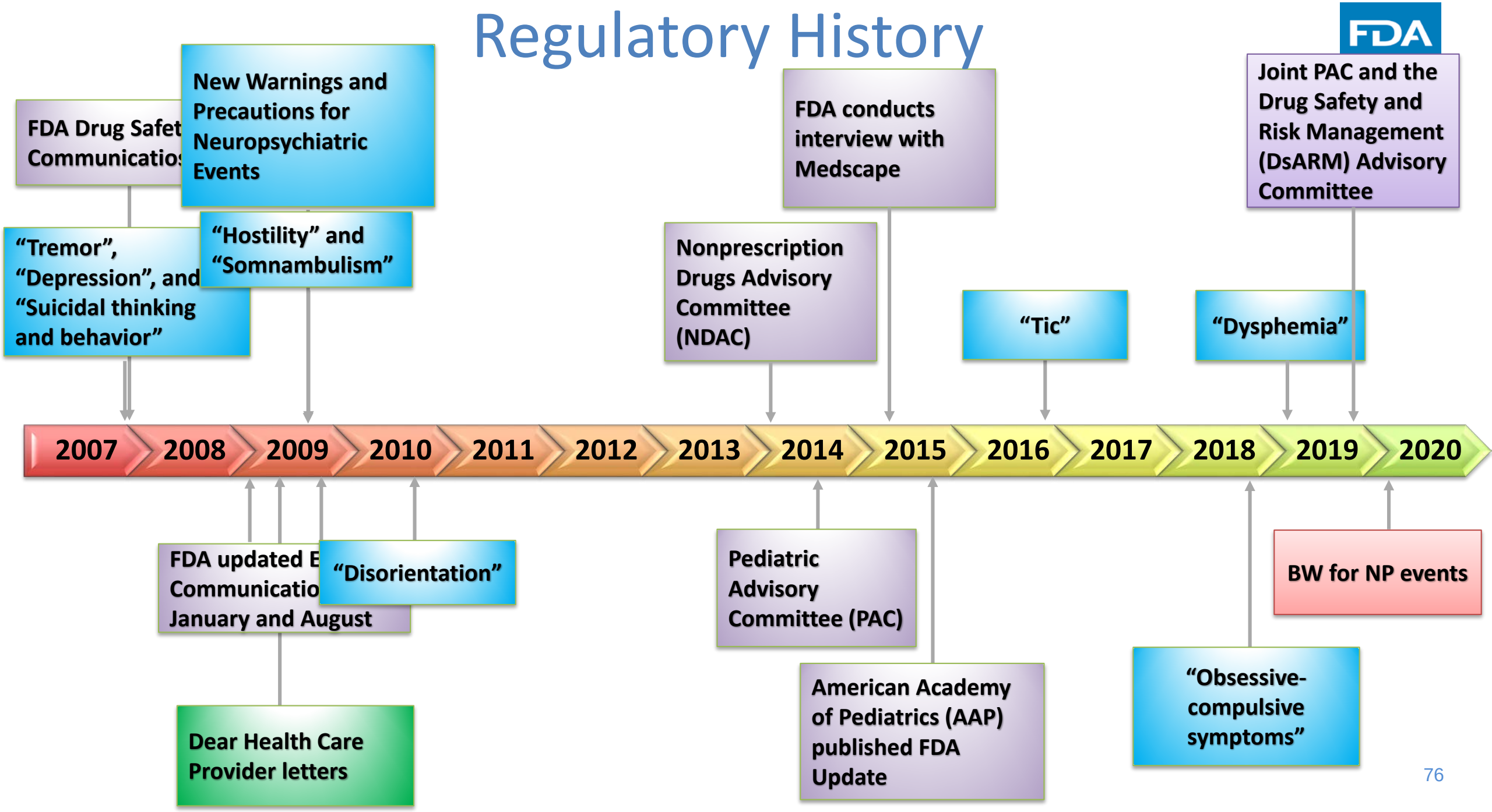
Montelukast Medication Guide

What is the most important information I should know about ?
Serious mental health problems have happened in people taking or even after treatment has stopped. This can happen in people with or without a history of mental health problems. Stop taking and tell your healthcare provider right away if you or your child have any unusual changes in behavior or thinking, including any of these symptoms:

- agitation, including aggressive behavior or hostility
- attention problems
- bad or vivid dreams
- depression
- disorientation (confusion)
- feeling anxious
- irritability
- hallucinations (seeing or hearing things that are not really there)
- memory problems
- obsessive-compulsive symptoms
- restlessness
- sleep walking
- stuttering
- suicidal thoughts and actions (including suicide)
- tremor
- trouble sleeping
- uncontrolled muscle movements

Prescribing Information

Regulatory History



Outline

- Product Information
- Neuropsychiatric Events and Safety Labeling
- Regulatory History Related to Neuropsychiatric Findings
- Regulatory Considerations
- Decision Making
- Updated Safety Labeling
- **Discussion Topics**
- Challenge Questions

Discussion Topics

1) Identify the spectrum of neuropsychiatric adverse events, including serious neuropsychiatric events associated with montelukast use.
2) List the different sources of safety data that contributed to the understanding of the risk of neuropsychiatric events with montelukast.
3) Describe the revised labeling recommendations for use of montelukast in patients with allergic rhinitis.

Outline

- Product Information
- Neuropsychiatric Events and Safety Labeling
- Regulatory History Related to Neuropsychiatric Findings
- Regulatory Considerations
- Decision Making
- Updated Safety Labeling
- Discussion Topics
- **Challenge Questions**

U.S. FOOD & DRUG ADMINISTRATION

Questions?

References

G. T. Schumock et al., Risk of suicide attempt in asthmatic children and young adults prescribed leukotriene-modifying agents: a nested case-control study. J Allergy Clin Immunol 130, 368-375 (2012).

V. C. Chen et al., Asthma and self-harm: a population-based cohort study in Taiwan. J Psychosom Res 77, 462-467 (2014).

M. M. Ali, C. E. O'Brien, M. A. Cleves, B. C. Martin, Exploring the possible association between montelukast and neuropsychiatric events among children with asthma: a matched nested case-control study. Pharmacoepidemiol Drug Saf 24, 435-445 (2015).

B. Benard et al., Neuropsychiatric adverse drug reactions in children initiated on montelukast in real-life practice. Eur Respir J 50, (2017).

FDA Pharmacology Review of Singulair. NDA 20829 (1998).

Y. Eriksson et al., The anti-asthmatic drug, montelukast, modifies the neurogenic potential in the young healthy and irradiated brain. Cell Death Dis 9, 775 (2018).

The Human Protein Atlas. Proteinatlas.org.

G. Burnstock, An introduction to the roles of purinergic signalling in neurodegeneration, neuroprotection and neuroregeneration. Neuropharmacology 104, 4-17 (2016).

U.S. Food and Drug Administration. FDA Briefing Materials for the September 27, 2019 Joint Meeting of the Pediatric and Drug Safety and Risk Management Advisory Committees. https://www.fda.gov/media/131035/download.

U.S. Food and Drug Administration. Transcript of the September 27, 2019 Joint Meeting of the Pediatric and Drug Safety and Risk Management Advisory Committees. https://www.fda.gov/media/132560/download.

U.S. Food and Drug Administration. "FDA requires Boxed Warning about serious mental health side effects fr asthma and allergy drug montelukast (Singulair); advises restricting use for allergic rhinitis." FDA Drug Safety Communication. March 4, 2020. Available at: https://www.fda.gov/drugs/drug-safety-and-availability/fda-requires-boxed-warning-about-serious-mental-health-side-effects-asthma-and-allergy-drug.

K. Clarridge, S. Chin, E. Eworuke, S. Seymour, A Boxed Warning for Montelukast: The FDA Perspective The Journal of Allergy and Clinical Immunology: In Practice, (2021).

V. Sansing-Foster et al., Risk of Psychiatric Adverse Events Among Montelukast Users. J Allergy Clin Immunol Pract 9, 385-393.e312 (2021).


FDA
U.S. FOOD & DRUG
ADMINISTRATION