FDA Joint Meeting of the Pediatric and Drug Safety and Risk Management Advisory Committees

Neuropsychiatric Events with the use of Montelukast in Pediatric Patients

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U.S. Food and Drug Administration
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Objectives

- Discuss ongoing concerns regarding neuropsychiatric adverse events with montelukast, particularly in pediatric patients
- Present FDA's review of available data and regulatory considerations
- Obtain input and recommendations from the Advisory Committees

FDA Agenda

- Background
- Pediatric Utilization Patterns
- Postmarketing Pharmacovigilance Review
- Risk of Neuropsychiatric Adverse Events
  - Literature
  - Sentinel
- Summary

FDA Presentation Outline

- Product Information
- Regulatory History Related to Neuropsychiatric Findings
- Current Review of Montelukast and Neuropsychiatric Events
- Regulatory Considerations
- Discussion Topics

Product Information

- Montelukast (Singulair)
- 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
- Multiple abbreviated new drug applications (ANDAs)

Approval History

- Tablets 10 mg: approved February 1998
- Tablets 4 mg, 5 mg: approved February 1998
- Chewable Oral Granules 4 mg: approved July 2002

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: Singulair Prescription Package Insert	

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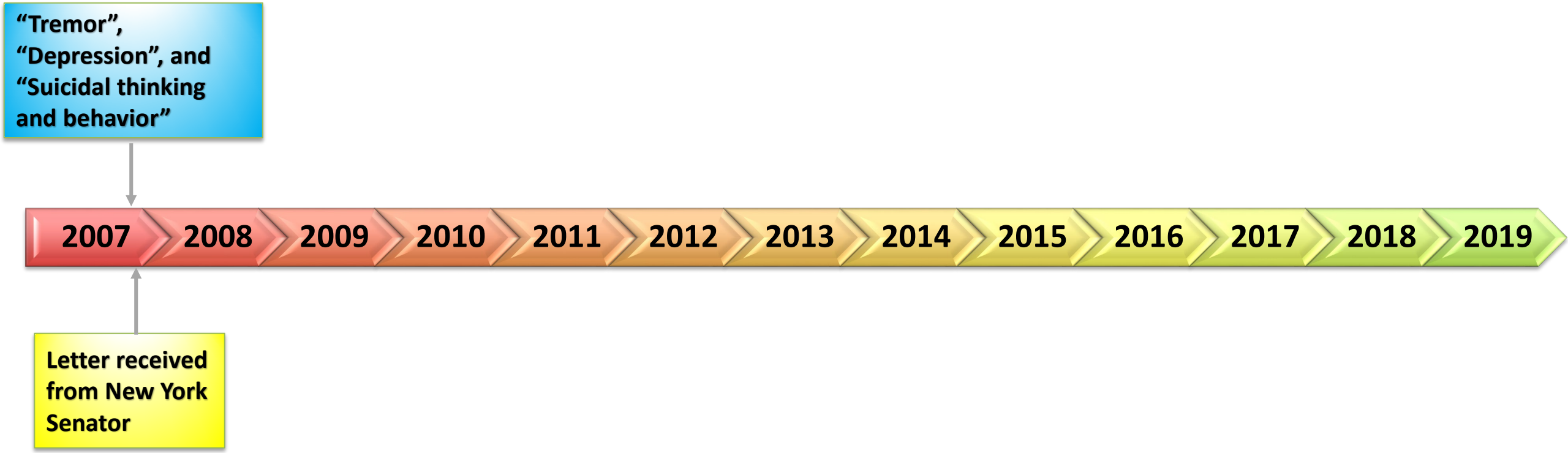
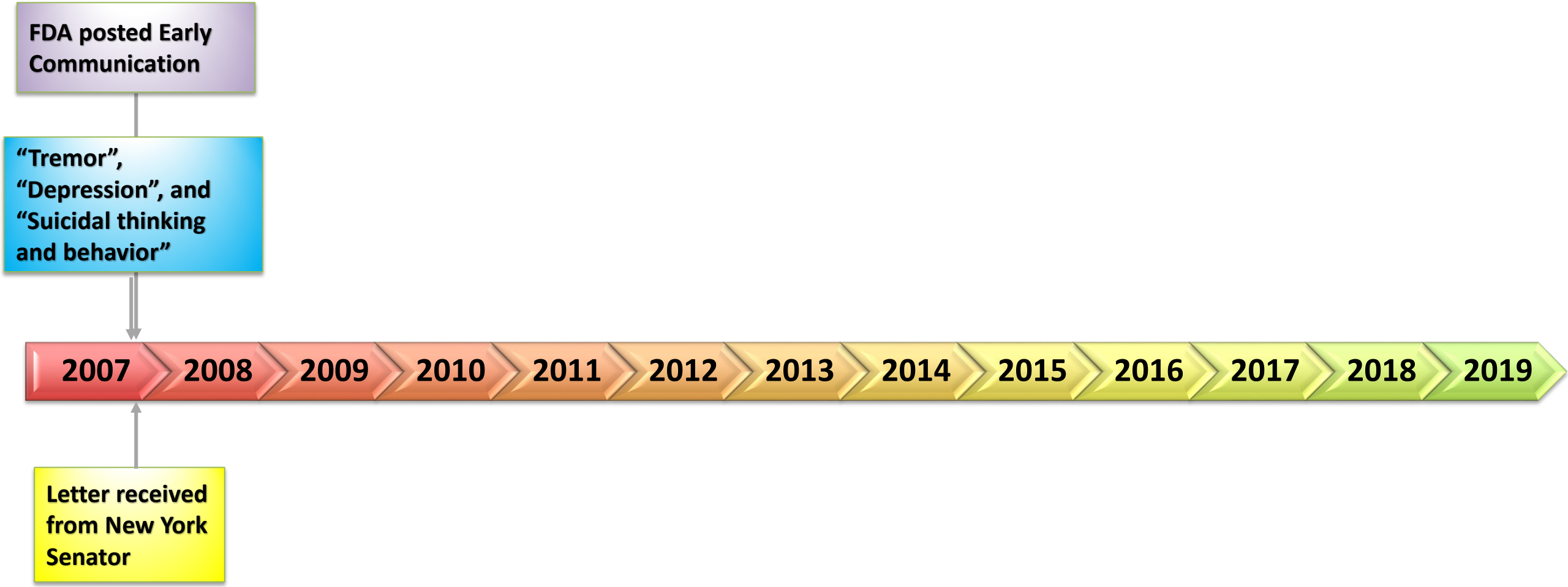
Regulatory History Related to Neuropsychiatric Adverse Events

Regulatory History



Regulatory History



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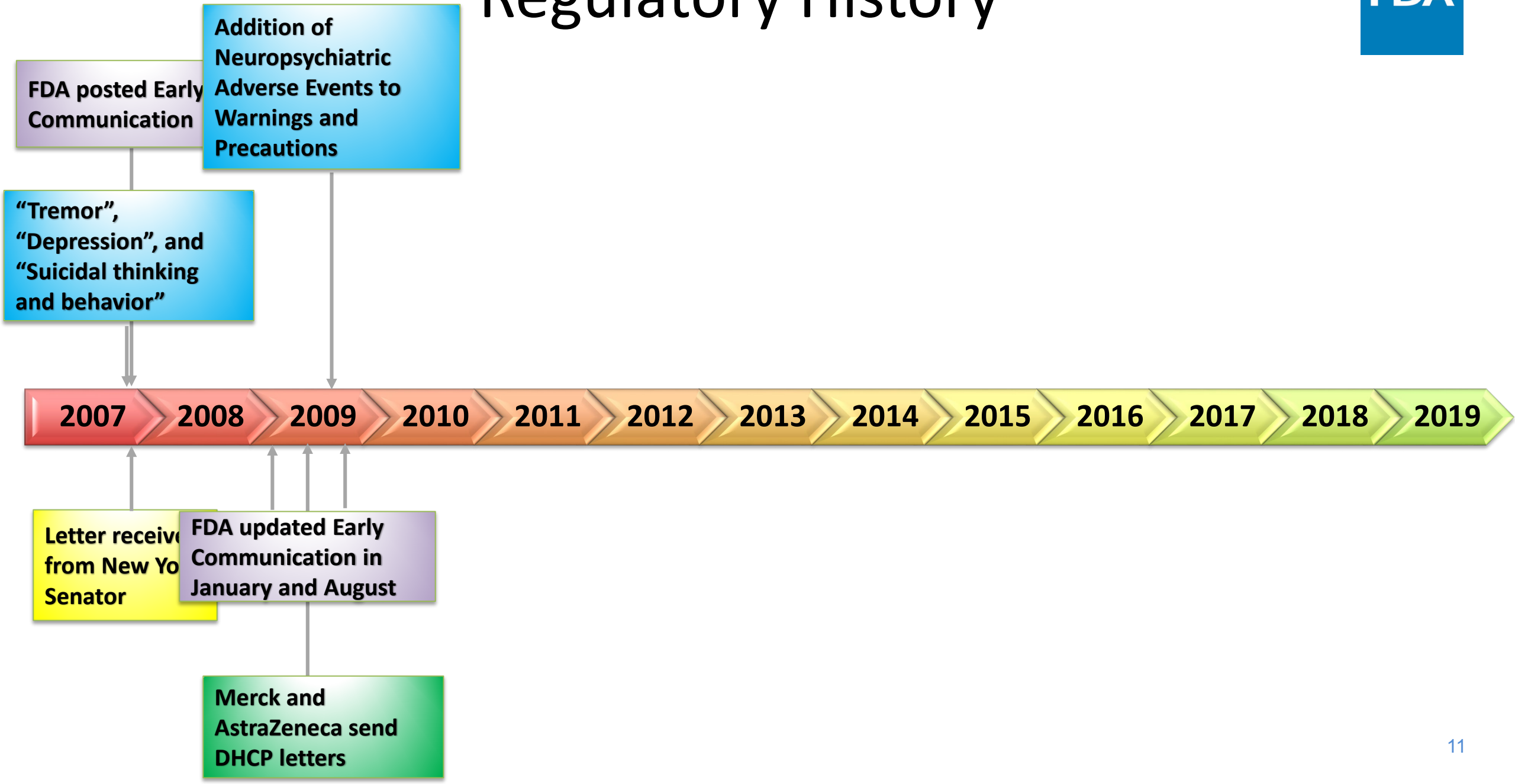

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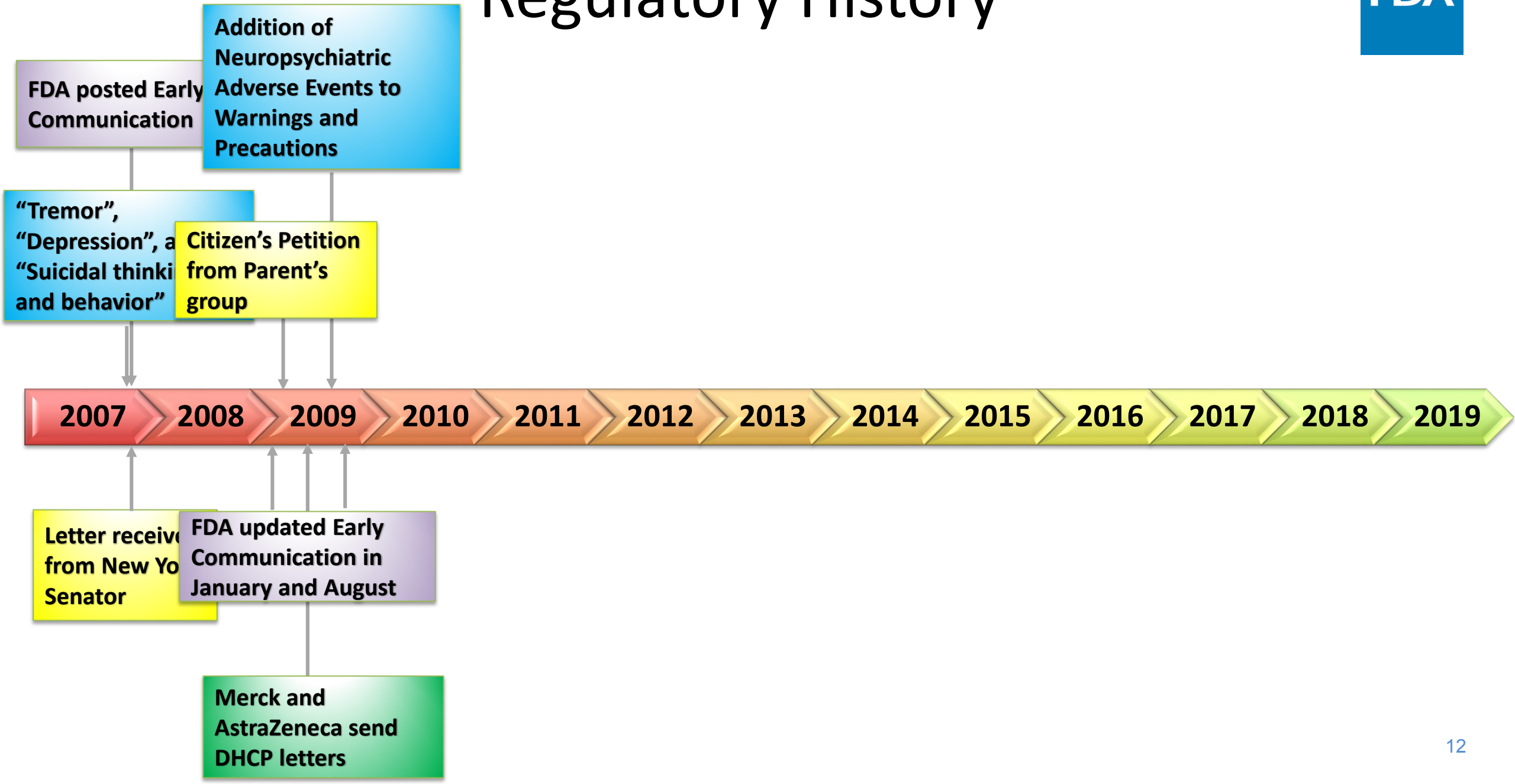

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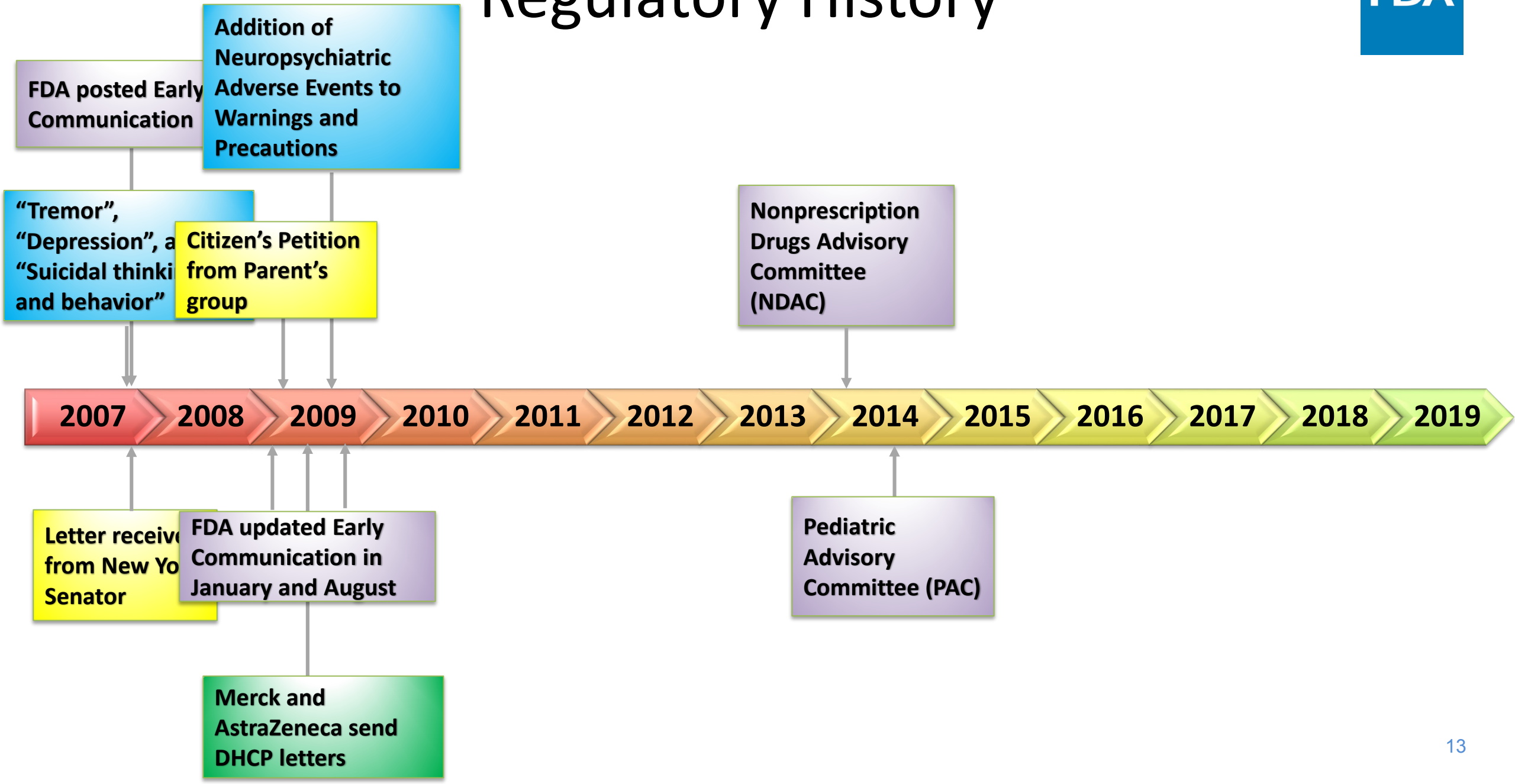

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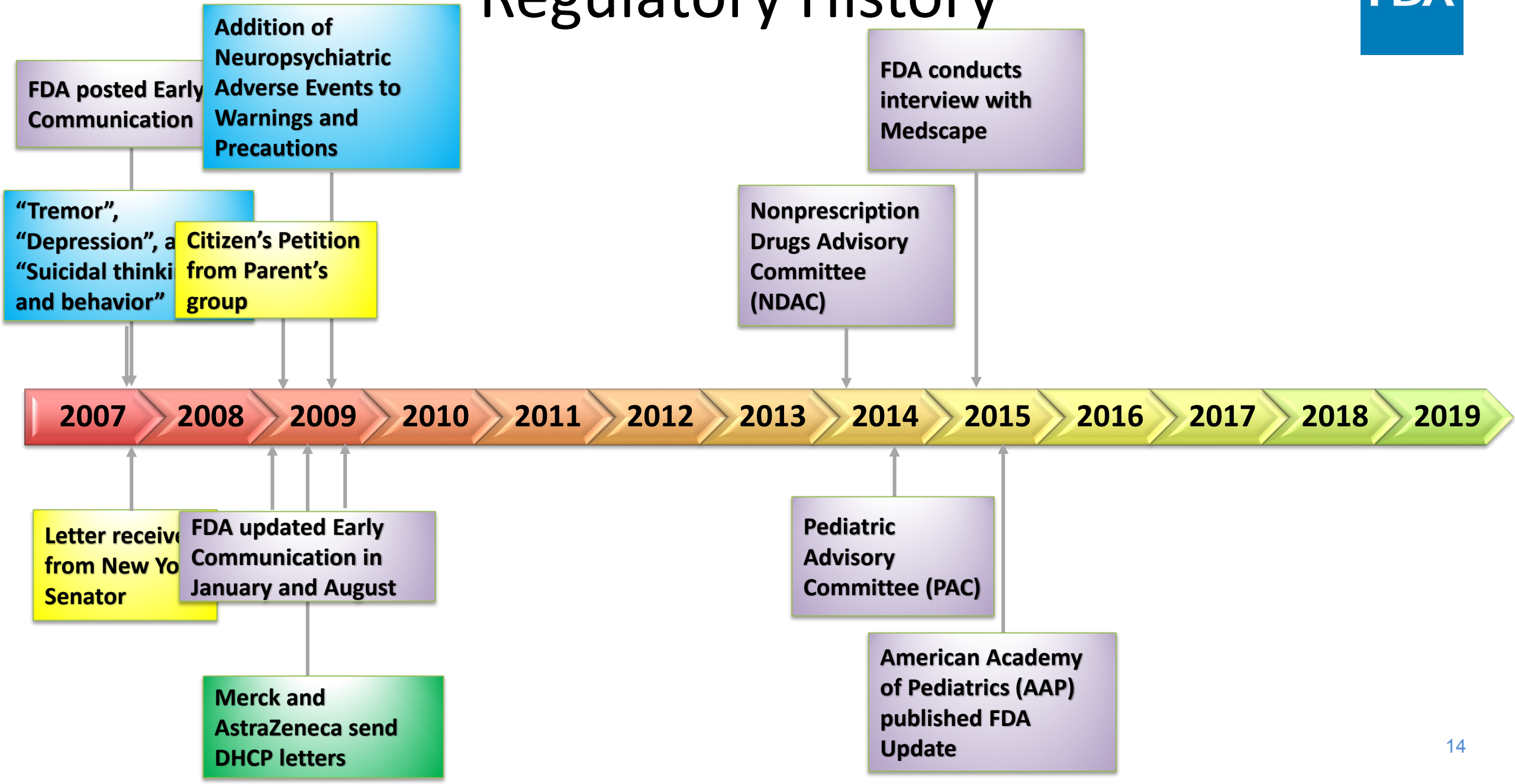
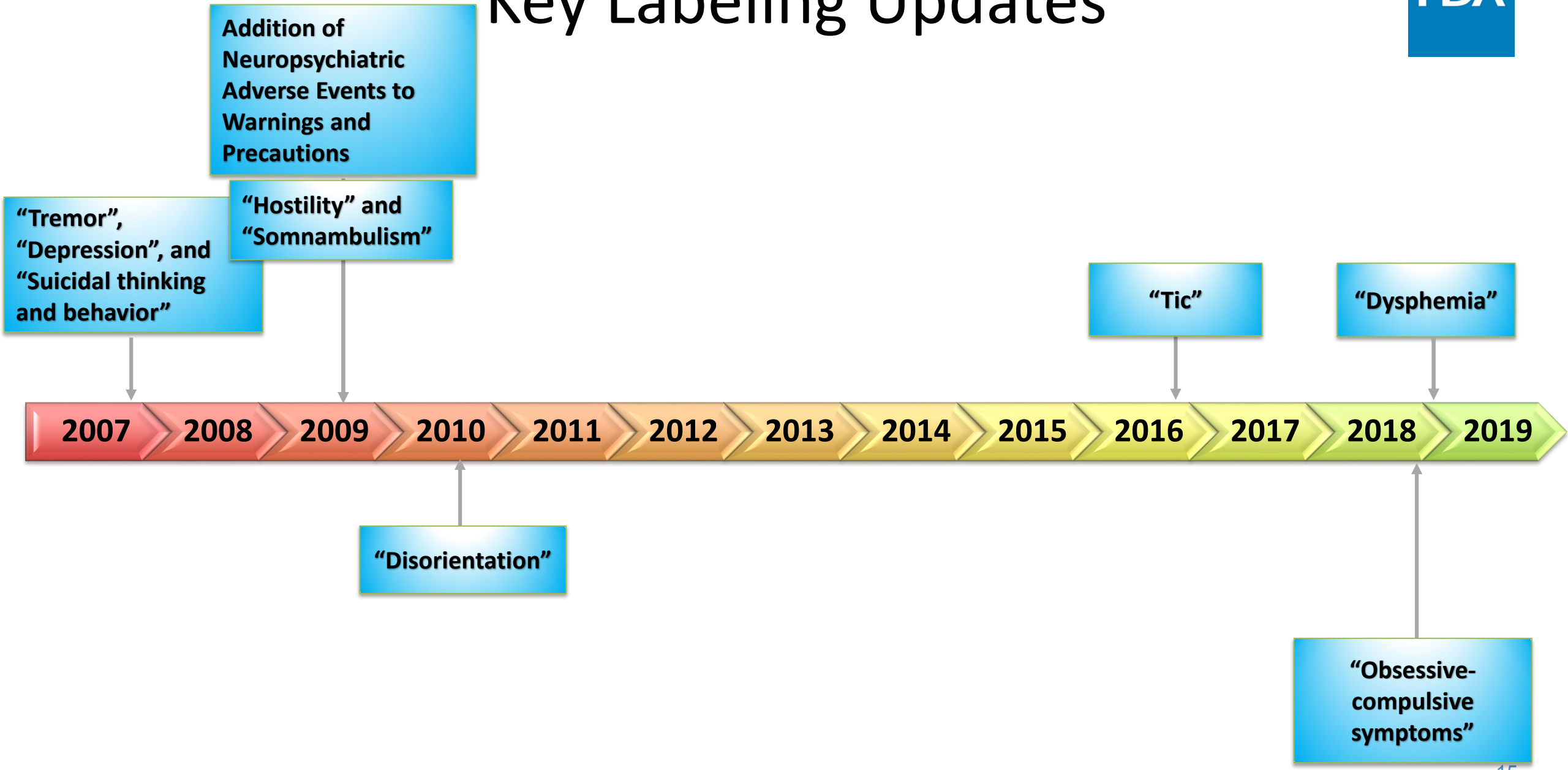


Key Labeling Updates



Montelukast Package Insert

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

5.4 Neuropsychiatric Events

Neuropsychiatric events have been reported in adult, adolescent, and pediatric patients taking SINGULAIR. Postmarketing reports with SINGULAIR use include, but are 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 thinking and behavior (including suicide), tic, and tremor. The clinical details of some postmarketing reports involving SINGULAIR appear consistent with a drug-induced effect. Patients and prescribers should be alert for neuropsychiatric events. Patients should be instructed to notify their prescriber if these changes occur. Prescribers should carefully evaluate the risks and benefits of continuing treatment with SINGULAIR if such events occur *[see Adverse Reactions (6.2)].*

Singulair (montelukast) Prescribing Information

Montelukast Patient Information

What are the possible side effects of SINGULAIR?

SINGULAIR may cause serious side effects.

- **Behavior and mood-related changes.** Tell your healthcare provider right away if you or your child have any of these symptoms while taking SINGULAIR:
  - agitation including aggressive behavior or hostility
  - attention problems
  - bad or vivid dreams
  - depression
  - disorientation (confusion)
  - feeling anxious
  - hallucinations (seeing or hearing things that are not really there)
  - irritability
  - memory problems
  - obsessive-compulsive symptoms
  - restlessness
  - sleep walking
  - stuttering
  - suicidal thoughts and actions (including suicide)
  - tremor
  - trouble sleeping
  - uncontrolled muscle movements

Singulair (montelukast) Prescribing Information

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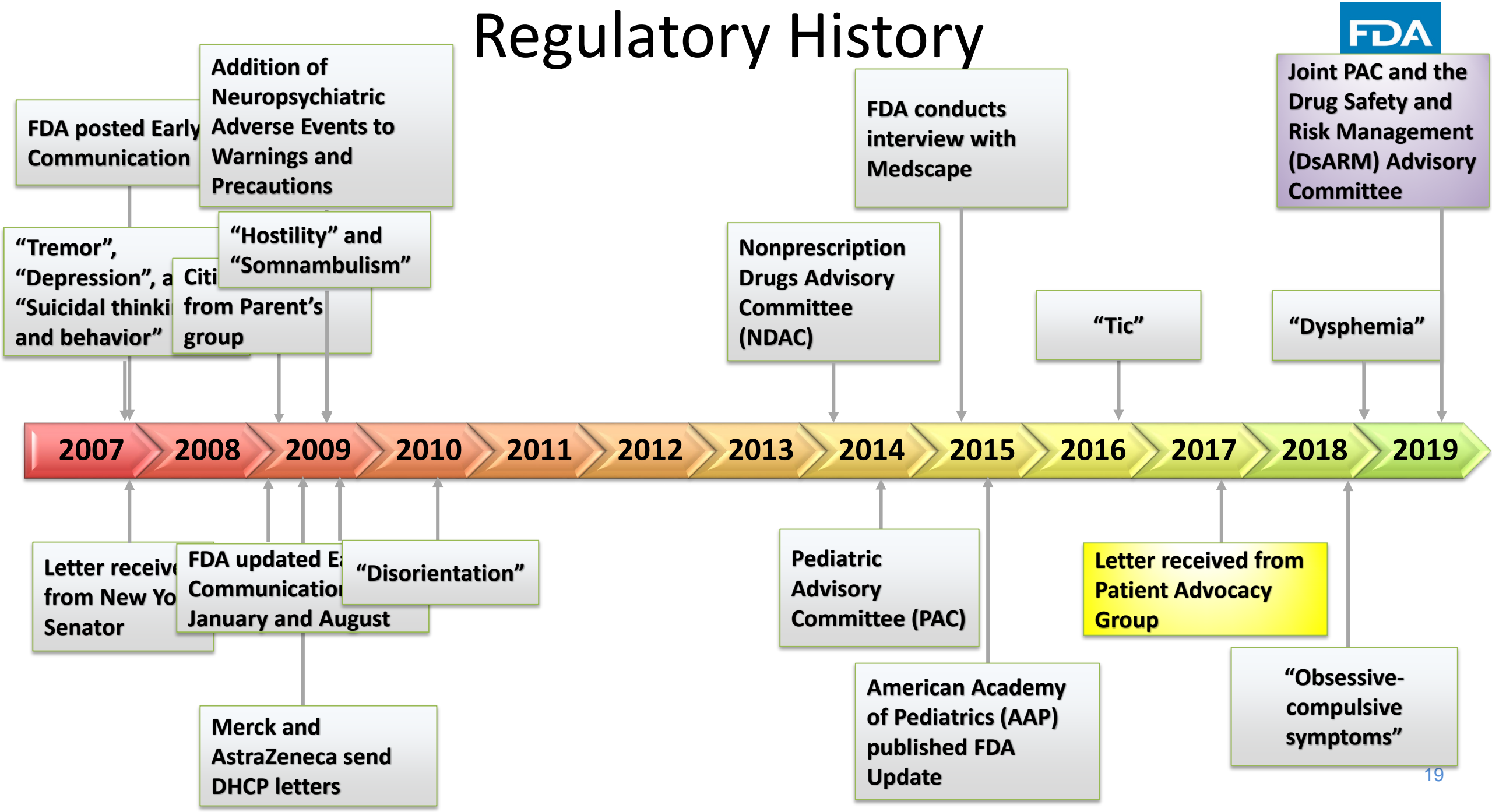

Letter from 2017

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

- Reviewed postmarketing pharmacovigilance data (FAERS)
- Reviewed observational literature
- Designed and conducted study in Sentinel
- Evaluated pediatric utilization patterns
- Reviewed nonclinical (animal) studies
- Explored communication strategies

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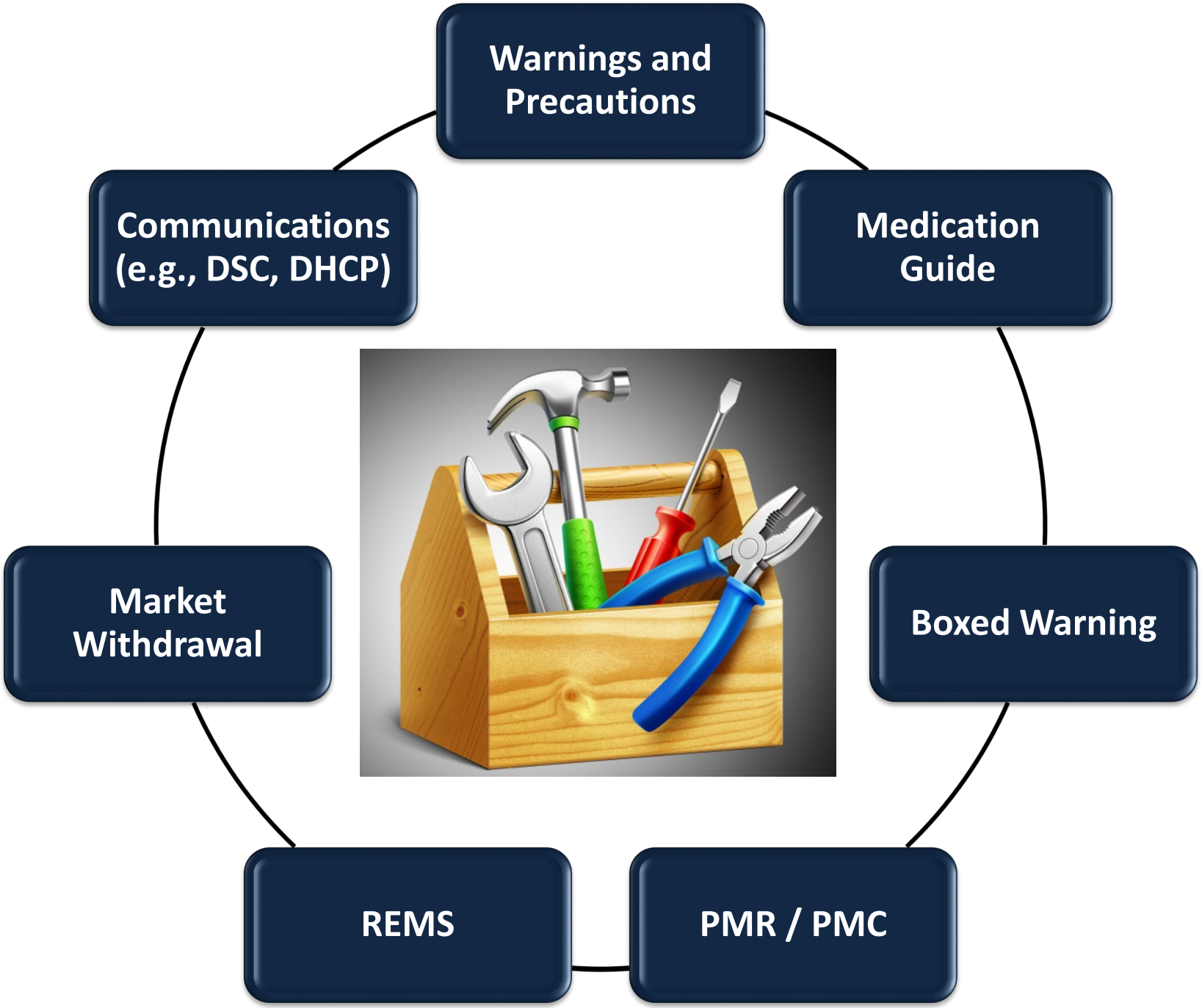
Warnings and Precautions
Medication Guide
Boxed Warning
PMR / PMC
REMS
Market Withdrawal
Communications (e.g., DSC, DHCP)

Labeling - Warnings and Precautions

- Product labeling conveys essential information for safe and effective use
- Neuropsychiatric Events are listed in the Warnings and Precautions section (5.4) of the label

Medication Guide

- FDA required patient labeling
- *21 CFR 208.1*
  - *Patient labeling could help prevent serious adverse effects*
  - *Serious risks (relative to benefits) of which patients should be made aware because information could affect decision to use the product*
  - *Patient adherence instructions for use is crucial to drug's effectiveness*

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*

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Discussion Topics

1) Neuropsychiatric safety findings presented for montelukast
2) Labeling for montelukast, including
   - Current Warnings and Precautions
   - Request for Medication Guide and Boxed Warning
3) Recommendations for communication strategies
   - Target audience
   - Target organizations
   - Modalities of communication


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