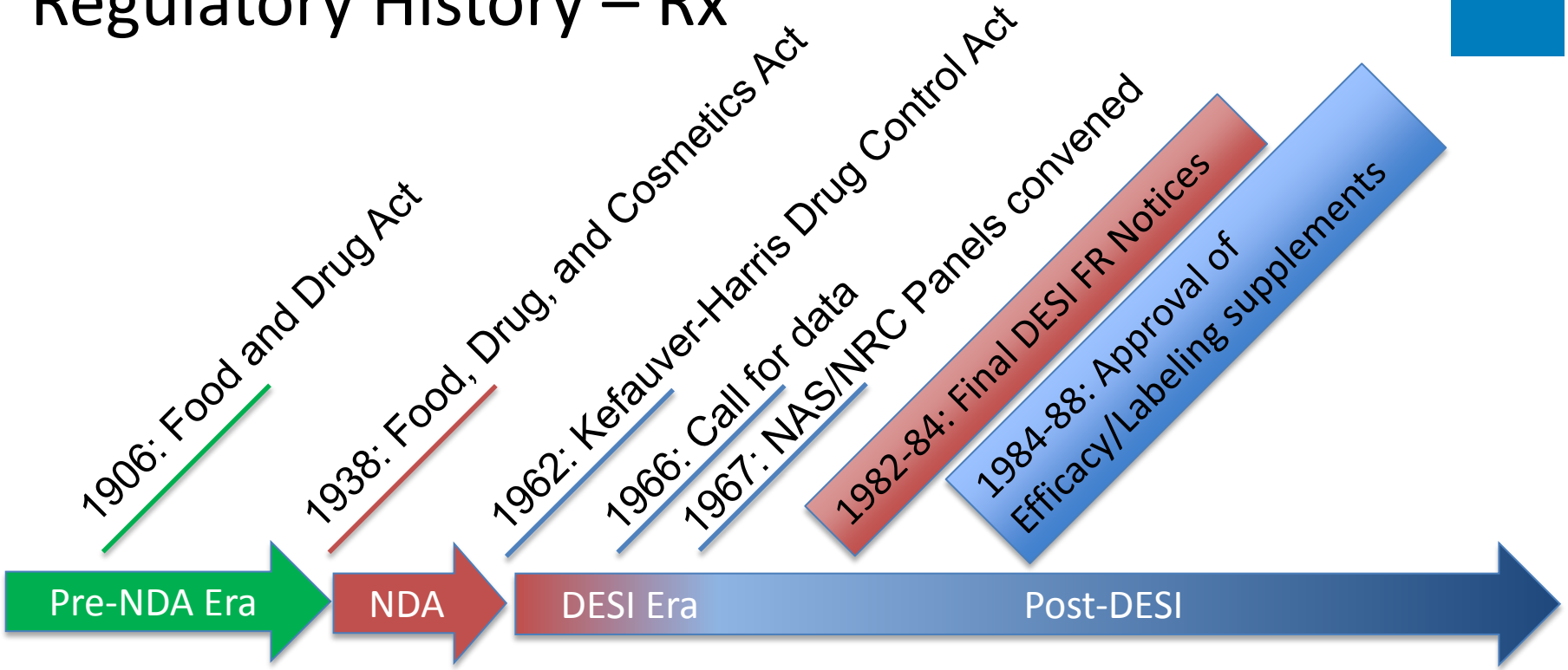
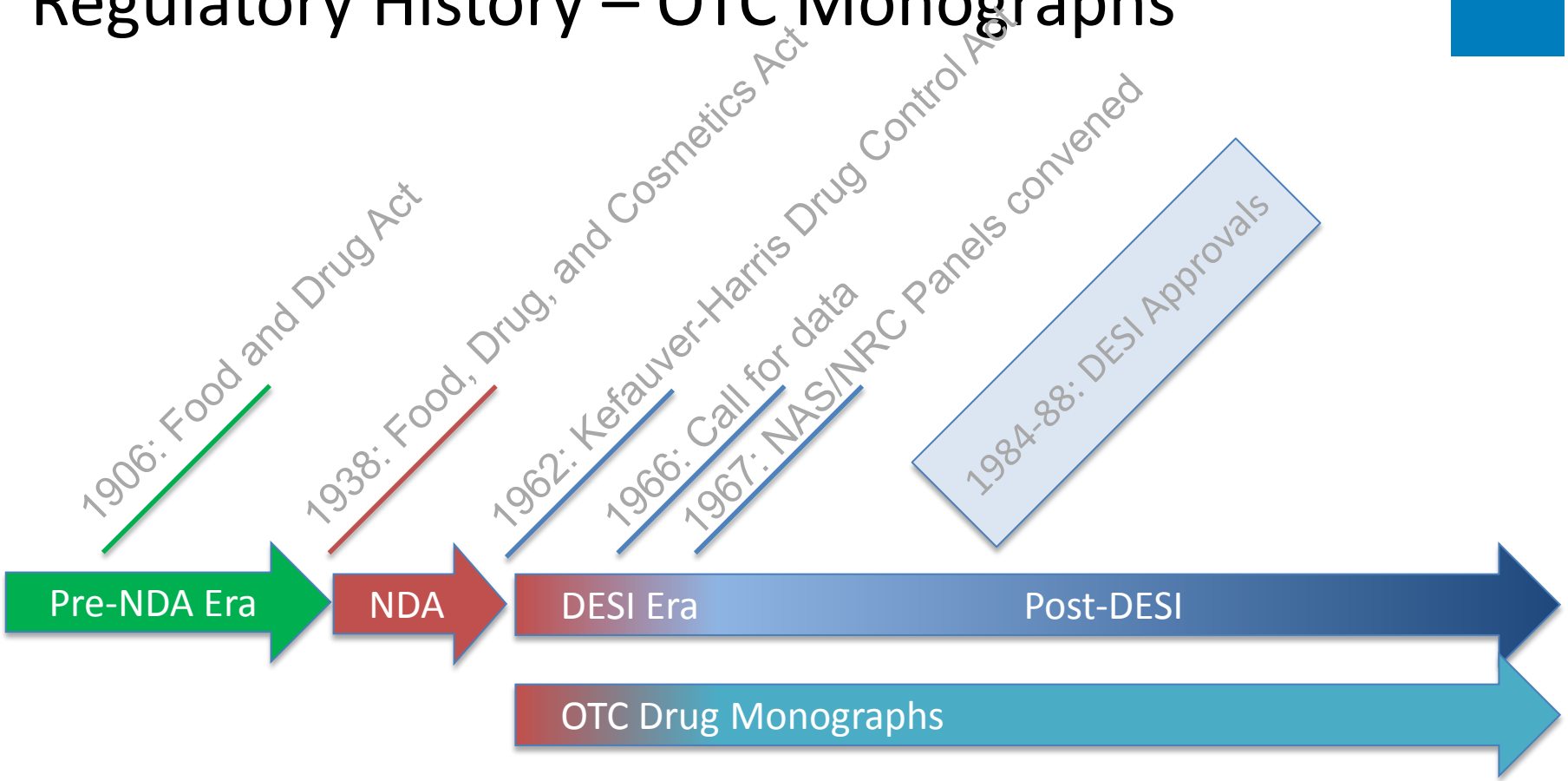
Regulatory History – Rx



- Hydrocodone (DESI effective 1982)
  + homatropine (1988)
  + chlorpheniramine (1987)
- Codeine (DESI effective 1984)
  + promethazine (1984)
  + promethazine and phenylephrine (1984)
  + triprolidine and PSE (1984)

Regulatory History – OTC Monographs



- Advisory Review Panels
  - Formed in 1972
  - Reviewed existing data and provided recommendations for monographs
- Monographs codified in the Code of Federal Regulations through rulemaking process
  - Codeine proposed for Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic (CCABA) Monograph

OTC CCABA Monograph Ingredients [1,2]

- Antitussives {21 CFR 341.14} [2]
  - Codeine
    - Limited to NMT 200 mg of codeine per 100 mL or per 100 gm [3]
    - Dosages for adults and children 6 years of age and older
    - Children under 6 years of age: “Consult a doctor”
    - Professional labeling / dosage for children 2 to under 6 years [4]
- Antihistamines {21 CFR 341.12} [2]
  - Includes chlorpheniramine and triprolidine
- Nasal decongestants {21 CFR 341.20}
  - Includes pseudoephedrine (PSE) and phenylephrine
- Expectorants {21 CFR 341.18}
  - Guaifenesin

1 21 CFR 341

2 Partial listing only

3 21 CFR 1308.15 provides that combinations containing codeine that have not more than (NMT) the specified quantity of codeine may be marketed as Schedule V drugs. 21 CFR 290.2 provides for an exemption from the prescription requirements for codeine when the preparation contains NMT the specified quantity of codeine and it is marketed in combination with other non-narcotic active ingredients.

4 21 CFR 341.90

OTC Monograph Concepts

- GRASE - “Generally recognized as safe and effective”
  - Ingredient may be marketed in products without the need for further evidence of efficacy or safety, if the product complies with monograph labeling and other conditions of use
- “Rational therapy” {21 CFR§330.10(4)(iv)} - Combinations are rational when:
  - Each ingredient contributes to the claimed effect(s)
  - None decreases the safety and effectiveness of the other ingredients
- Permitted combinations {21CFR§341.40}
  - Example: antitussive + antihistamine
- Principles applied to the prescription setting
  - Efficacy of codeine as an antitussive
  - Efficacy and safety (GRASE) of monograph ingredients in combinations (e.g., antihistamines, decongestants, expectorants)
  - Rational therapy and permitted combinations
  - Clinical trials not required; establish bioequivalence
  - Labeling and dosage based upon monograph and DESI ingredients

Prescription Opioid Antitussive Products – DESI Supplements and NDAs (currently marketed)

Hydrocodone

+ homatropine (1943)
+ chlorpheniramine (1987)

Codeine

+ promethazine (1952)
+ promethazine and phenylephrine (1952)
+ triprolidine and PSE (1960)

Blue = Over-the-counter (OTC) monographed (CCABA)

Red = Non-monographed

Dates are for approval of the new drug application, not DESI supplement approval

Prescription Opioid Antitussive Products – Approved and Currently Marketed

Hydrocodone

+ homatropine (1943)
+ chlorpheniramine (1987, 2013)
+ chlorpheniramine and pseudoephedrine (PSE) (2011)
+ PSE (2011)
+ guaifenesin (2014 & 2015)
+ guaifenesin and PSE (2015)

Codeine

+ promethazine (1952)
+ promethazine and phenylephrine (1952)
+ triprolidine and PSE (1960)
+ chlorpheniramine (2015)

Blue = Over-the-counter (OTC) monographed (CCABA)

Red = Non-monographed

Dates are for approval of the new drug application, not DESI supplement approval

Outline

- Background

- Regulatory History
  - Drug Efficacy Study Implementation (DESI)
  - Prescription (Rx)
  - Over-the-Counter (OTC) Monograph

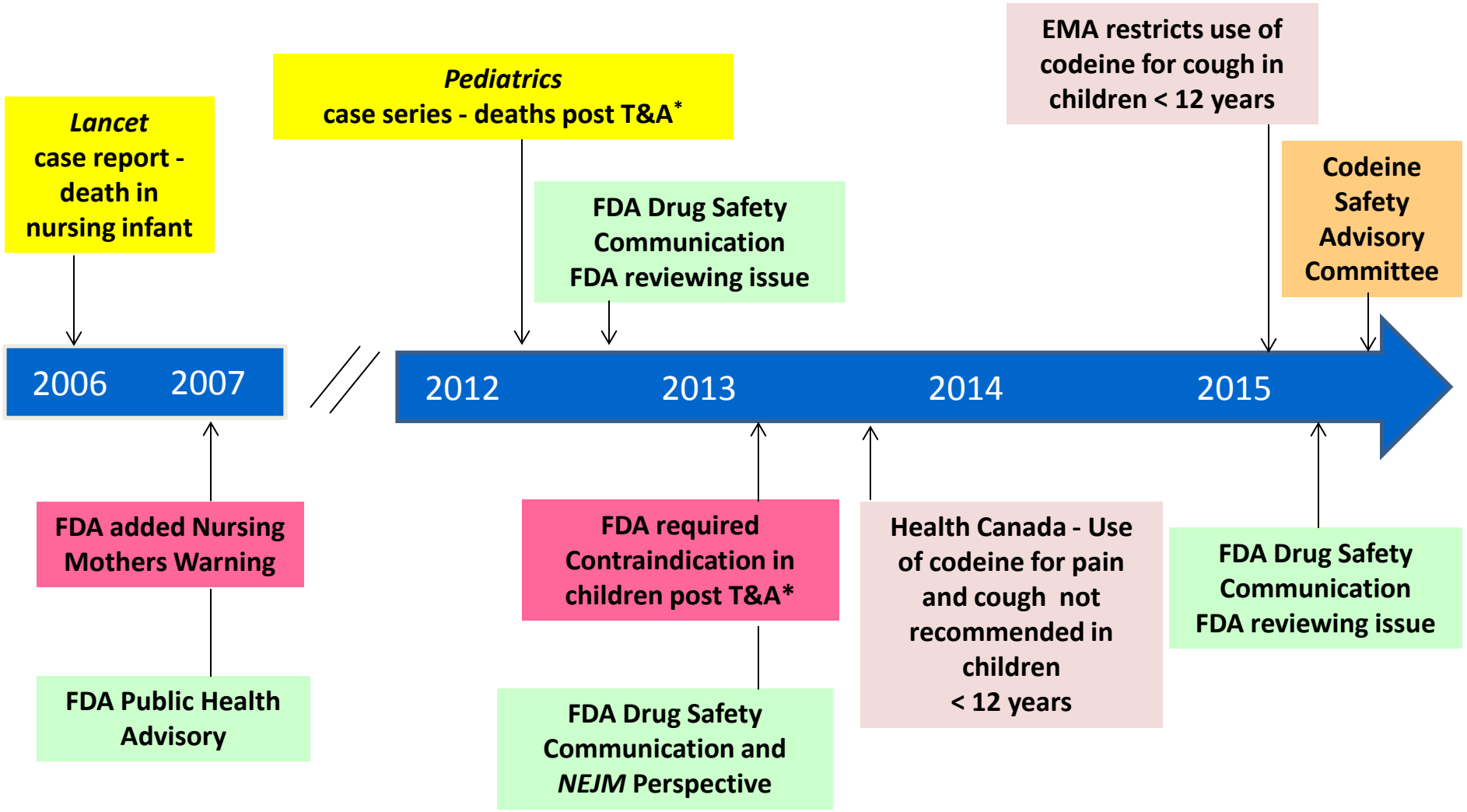
- Recent Regulatory Activities

- Alternative Products
  - Non-opioid antitussives

Regulatory Safety Activities – 2006 to 2015
Codeine Safety Labeling

- Codeine
  - Converted by CYP2D6 to morphine (active metabolite)
  - Significant genetic variability in CYP2D6 activity
    - Ultrarapid metabolizers → toxicity
    - Poor metabolizers → little or no benefit
- Respiratory Depression and Death
  - Breastfeeding infants
  - Young children, particularly post tonsillectomy
- FDA-required safety labeling
  - Boxed Warning: Ultrarapid metabolism / CYP2D6 / Respiratory Depression and death
  - Warning for nursing mothers: Breastfeeding not recommended
  - Contraindication: Children younger than 18 years of age post tonsillectomy/adenoidectomy

Regulatory Safety History – 2006 to 2015
Codeine Safety



* T&A = Tonsillectomy and Adenoidectomy

Regulatory Safety History – December 2015 Codeine Safety AC Meeting

- Discussion: Panel discussed available safety data with codeine used for cough [and analgesia]
- Voting: Age for a Contraindication for codeine use for the treatment of cough in children
  - Children < 6 years of age – 1 vote
  - Children < 12 years of age – 5 votes
  - Children < 18 years of age – 20 votes
  - No change – 3 votes
- Recommendation: Committee recommended removal of codeine from the OTC CCABA Monograph

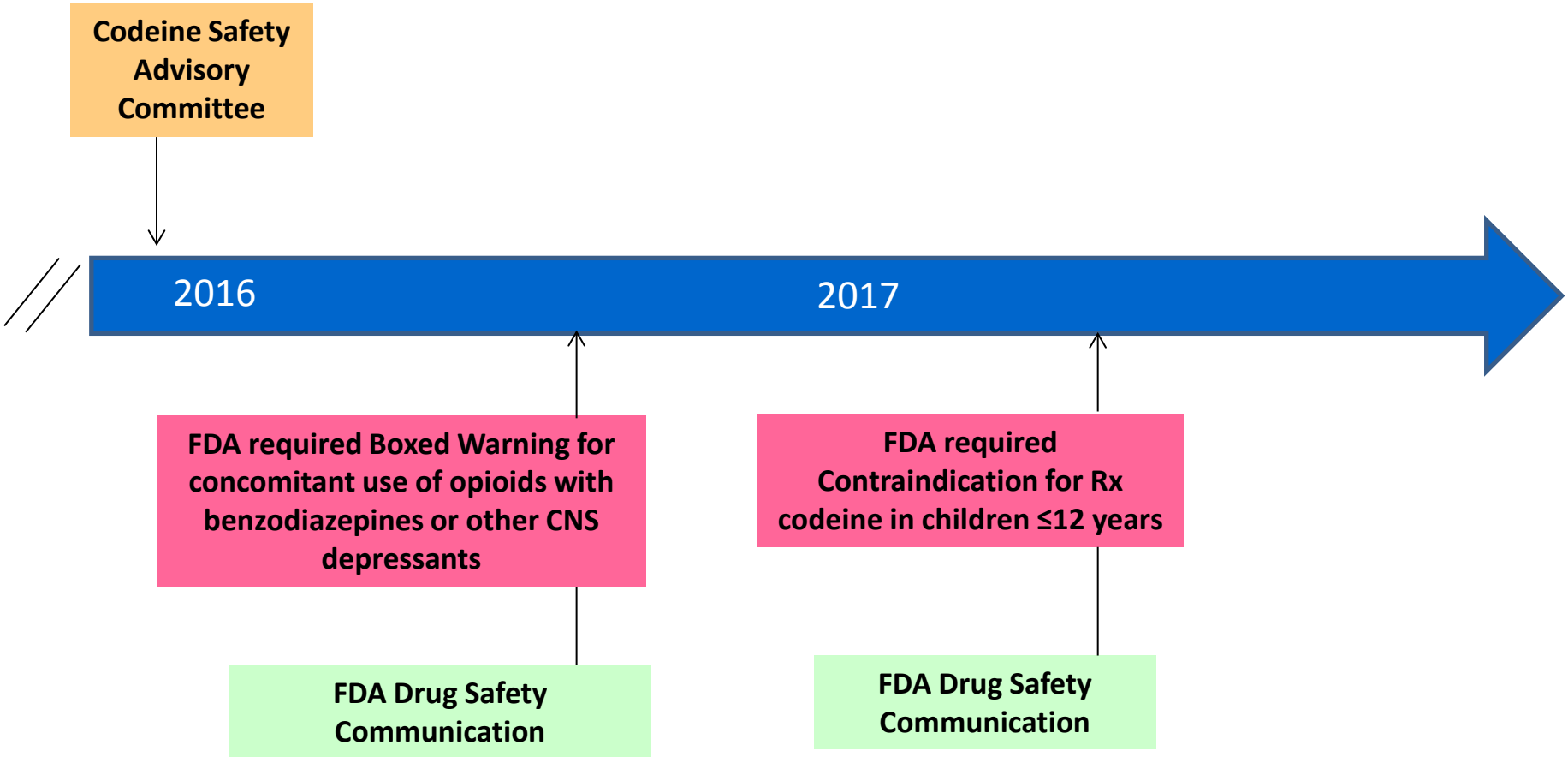
Regulatory Safety Activities – 2015 to date
Opioid Safety Labeling

- Respiratory Depression and Death
  - Vulnerable populations
    - Young children
    - Elderly
  - Extended-release formulations
  - When combined with other drugs that may be associated with respiratory depression
    - Benzodiazepines
    - CNS depressants
    - Alcohol
    - Promethazine
- New FDA-required safety labeling – all opioids
  - Boxed Warning: Benzodiazepines or other CNS depressants, including alcohol (opioid antitussive labeling approved January 13, 2017)

Regulatory Safety Activities – 2015 to date
Codeine Safety Labeling

- New FDA-required safety labeling – codeine
  - Contraindication: For the use of codeine for pain or cough in patients less than 12 years of age
    - majority of cases were in this age group
  - Warning: Regarding use in adolescents between 12 and 18 who have risk factors for respiratory depression, e.g. obesity, obstructive sleep apnea (OSA)
  - Strengthened Warning: Breastfeeding is not recommended with use of codeine
  - Supplements required April 20, 2017; approved August 29, 2017

Regulatory Safety History – 2015 to date
Opioid Safety



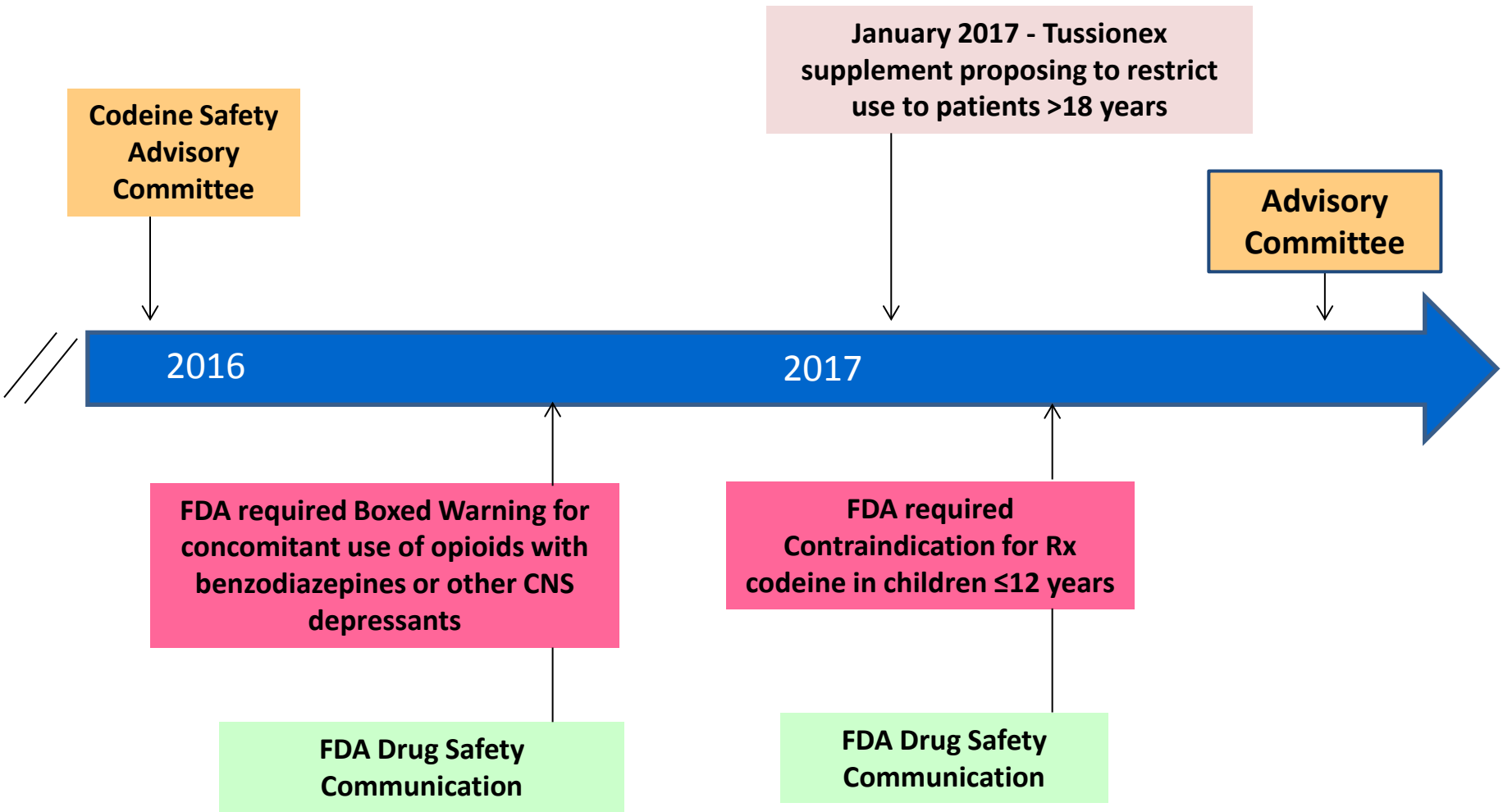
Tussionex Labeling Proposal

- Tussionex: Hydrocodone polistirex and chlorpheniramine polistirex extended-release suspension
- Labeling supplement (January 2017)
- Proposal:

  Limitation of Use

  – Tussionex not indicated for patients under 18 years of age
- Rationale
  – Existing concerns about safety of opioid use in children
  – Prevalence of abuse of prescription opioid medications
  – Known serious adverse events with opioid antitussives in children
  – Benefit/risk assessment for Tussionex is not favorable for the treatment of acute cough in pediatric patients

Regulatory Safety History – 2015 to date
Opioid Antitussives



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Prescription Antitussives

Active Ingredient	Class	Age	Relevant Labeling
Benzonatate Perles and Capsules (1958)	Peripheral anesthetic	≥10 years	• Do not break, crush, chew: Warning: Severe hypersensitivity reactions (including bronchospasm, laryngospasm and cardiovascular collapse)… possibly related sucking or chewing the capsule • Temporary local anesthesia • Accidental ingestion resulting in death has been reported in children <10 years of age • Dosing information for children 10 years and older

Over-the-Counter Antitussives – Oral Products

Active Ingredient	Class	Age	Relevant Labeling
Chlophedianol hydrochloride	Centrally Acting	≥6 years	• Non-narcotic for temporary relief of cough • Do not take for chronic cough • Children <6 years: Consult a doctor • OTC Monograph also contains professional labeling for dosing in children 2 to <6 years
Dextromethorphan Dextromethorphan hydrobromide	Centrally Acting	≥2 years	• Non-narcotic for temporary relief of cough • Do not take for chronic cough • Children <2 years: Consult a doctor
Diphenhydramine Diphenhydramine hydrochloride	Antihistamine / antitussive	≥6 years	• Non-narcotic for temporary relief of cough • May cause marked drowsiness • Alcohol, sedatives, and tranquilizers may increase sedative effect • Do not give to children <12 years of age who have a breathing problem • Children <6 years: Consult a doctor • OTC Monograph also contains professional labeling for dosing in children 2 to <6 years

Over-the-Counter Antitussives – Topical Products

Active Ingredient	Class	Age	Relevant Labeling
Camphor Menthol	Topical (ointment, lozenge, steam inhalation)	≥2 years	• Topical: For external use only • Flammability: Safety concern about fire-related events when ointment vehicle or alcohol-based solutions are placed in hot water or heated in microwave • Children <2 years: Consult a doctor

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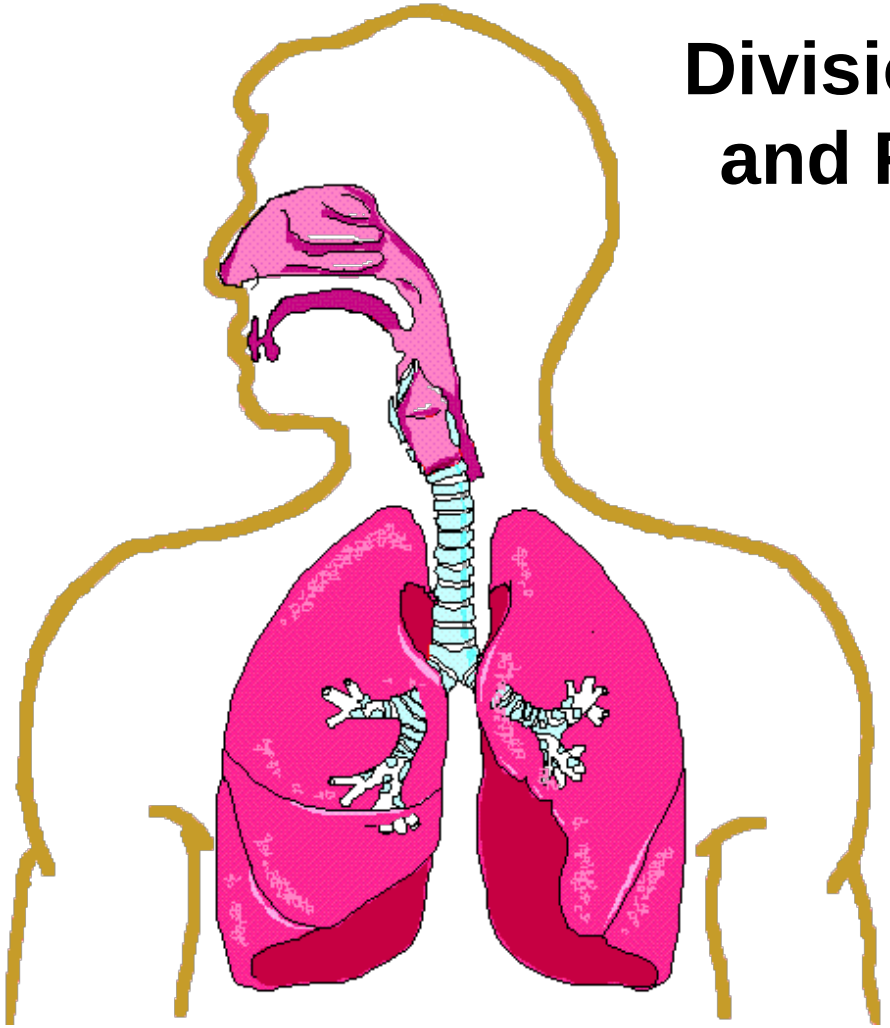

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