Prospects for a Disease Modifying Claim in Neurodevelopmental Disorders

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Disclaimer

- This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.

When Last We Met…

- Presentation to ISCTM in 2014
  - Dr. Robert Levin outlined FDA's perspective on disease-modifying claims for schizophrenia
  - Outlined several definitions of disease modification
  - Proposed a "gold standard"
  - Provided examples of disease modification claims in several non-psychiatric illnesses
  - Described some study designs with potential for evaluating disease modification claims

So, where are we now?

Since 2014

- No drugs approved with disease modifying claims in psychiatry
- To my knowledge, no studies have been conducted using a delayed start design for any psychiatric indication
- No broad Agency guidance on disease modification

Challenges for Disease Modifying Claims in Psychiatry

- As outlined by Dr. Levin in 2014:
  - What are the pathophysiological processes?
  - Is it a progressive disease or illness? Course, trajectory, rate? Heterogeneous clinical courses and probably heterogeneous underlying pathophysiology, at different phases of illness
  - Progression in everyone or subgroups? Identify patients & groups who will deteriorate.
  - Which aspects of D/O and DZ are progressive? Positive Sx, Negative Sx, Cognitive impairment (specific), general deterioration of functioning or specific functional impairments?
  - When to study progression? How long to study?
  - What type of study designs?

Challenges for Disease Modifying Claims in Psychiatry

- Primary issue: What is the disease?
  - DSM defines *syndromes*, not diseases
  - Relationship between symptoms and pathophysiology poorly understood

Image: American Psychiatric Association

Simplified Model of Humans and Diseases

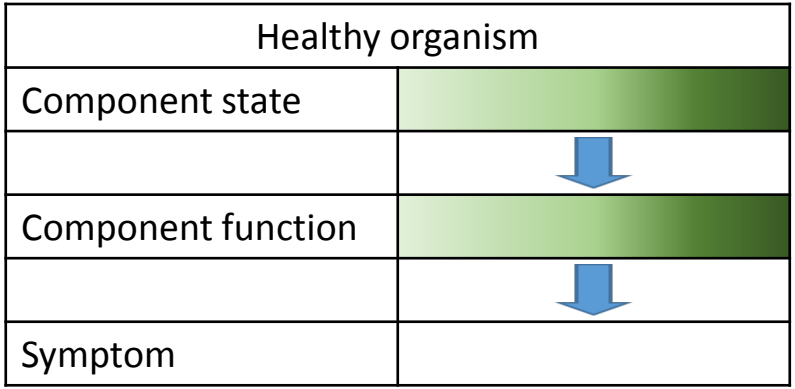
- Human is a collection of interacting biological components
  - Genes, regulatory networks, cells, organs
- Certain changes in a component's state changes the component's functioning
- Change in function at the component level may be observable as a change in function at the organism level

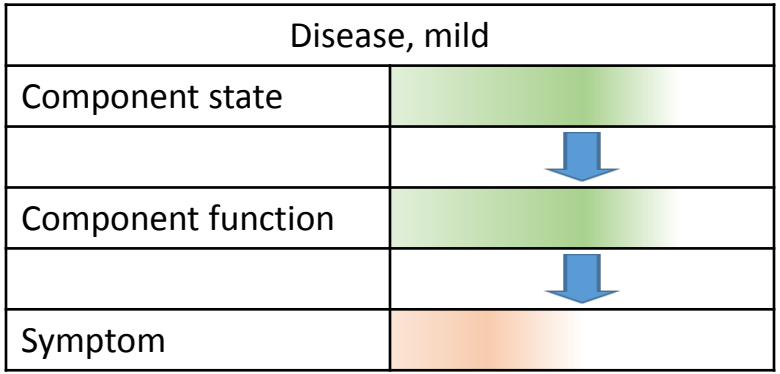
Type of change	Interpretation
State change at component level	Disease etiology
Function change at component level	Disease
Function change at organism level	Symptom

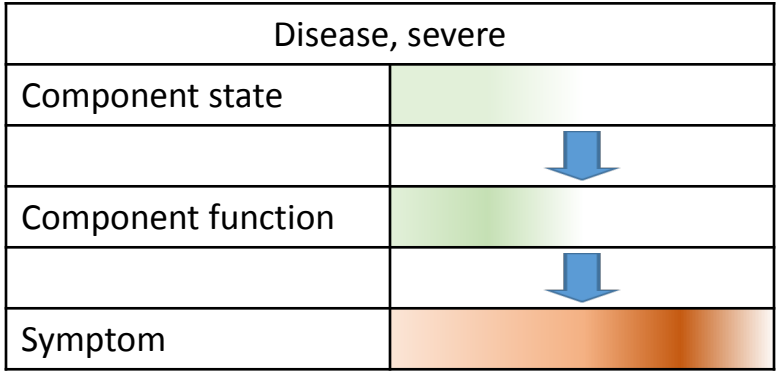
What Makes a Disease Modifiable?

- A component that can undergo a state change
  - Anatomical structure
  - Cell structure
  - Gene sequence
  - Gene regulatory network
- Disease manifestations
  - Symptom (change in function at a point in time)
  - Course (change in function over time)
- Relational elements
  - Connections or links between state changes and manifestation
  - Relations represent causality and not just co-occurrence

Healthy and Disease States when Disease Etiology is Related to a Single Component







Key Elements of This Model

- The relationships between component state and component function, and between component function and symptoms, are causal relationships, not just co-occurrence
- Our state of knowledge about these relationships is a key element in designating a drug's action as disease modification
- Observation of a change in syndrome course, in the absence of an understanding of the underlying mechanism of symptom causation, is insufficient for a disease modification claim
  - This is a clarification in our thinking since the 2014 ISCTM presentation

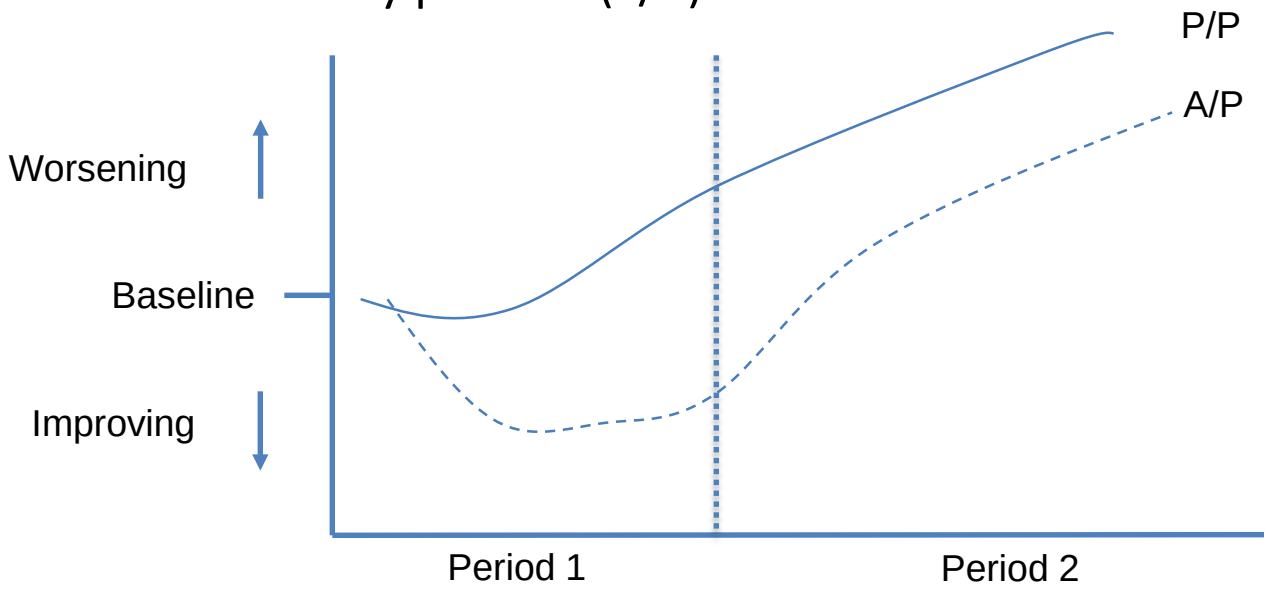
Neurodevelopmental Disorders

- Multiple aspects of development usually affected
- Complex pathophysiology
  - More than 1000 genes have been associated with autism spectrum disorder
  - Fragile X Syndrome caused by single gene mutation, but results in complex pattern of physical and intellectual changes
- Potential effects of disease modifying treatments depend on both the nature and the timing of the intervention

Image: Centers for Disease Control and Prevention

Trial Designs to Assess Disease Modification Claims

- Withdrawal Design
  - Subjects randomized to active treatment followed by placebo (A/P) vs. placebo followed by placebo (P/P)



Trial Designs to Assess Disease Modification Claims

- Randomized Delayed Start
  - Subjects randomized to 1) active treatment followed by active treatment or 2) placebo followed by active treatment

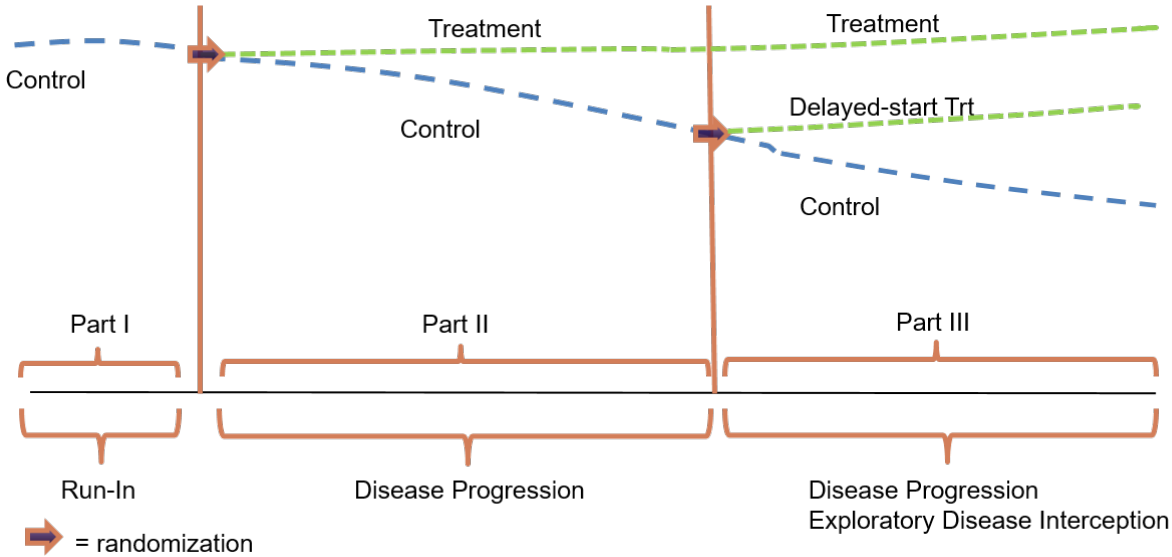
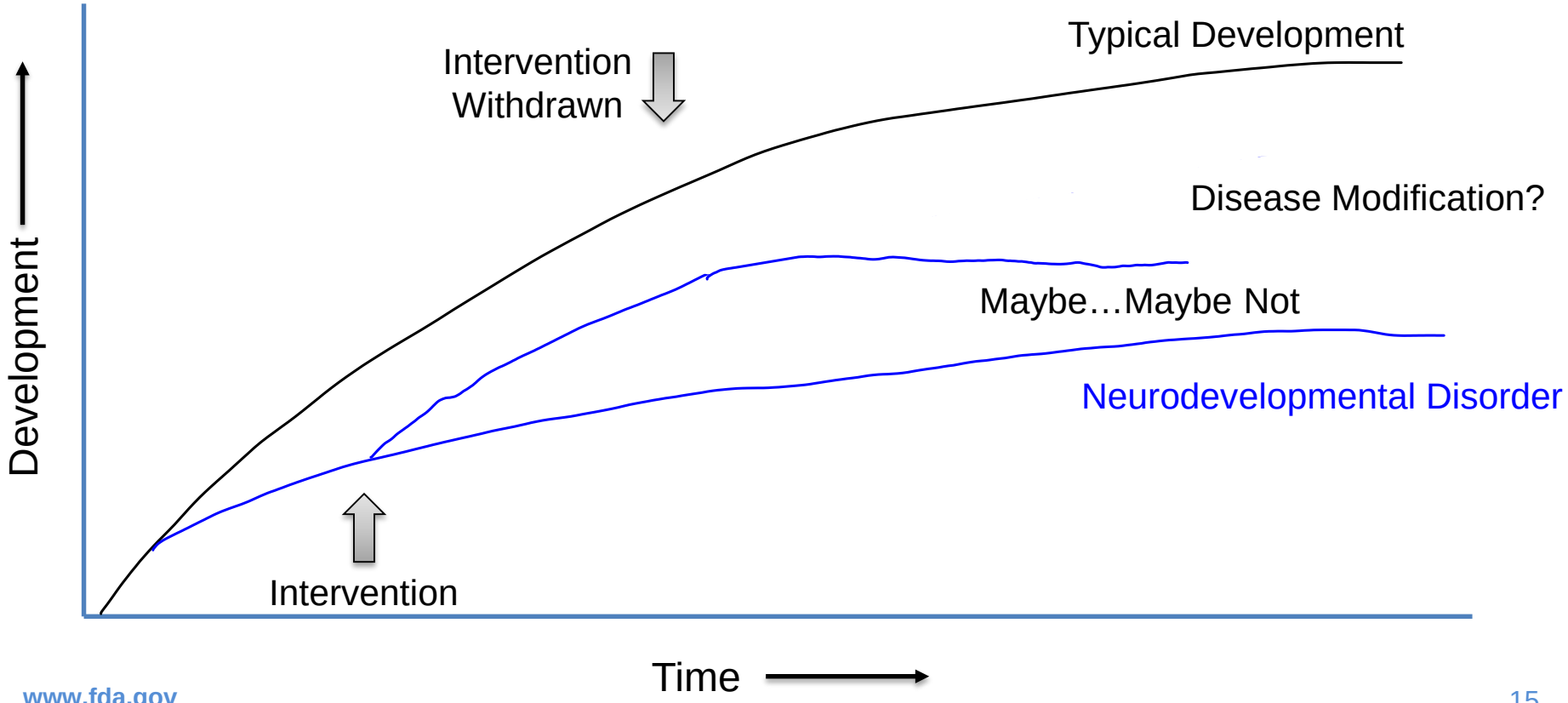
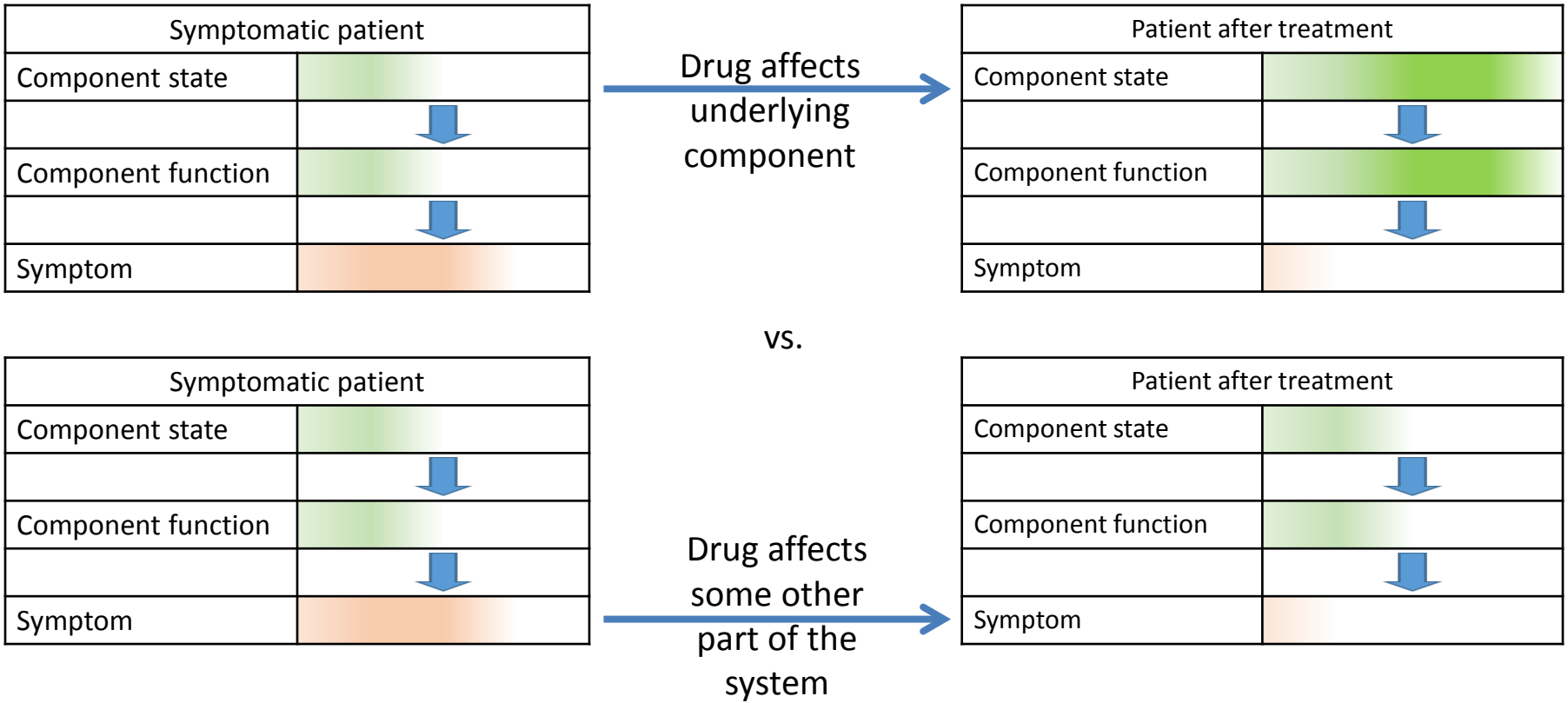


Image adapted from Dr. Turkoz's presentation

Addressing a Moving Target



How to Interpret Withdrawal?



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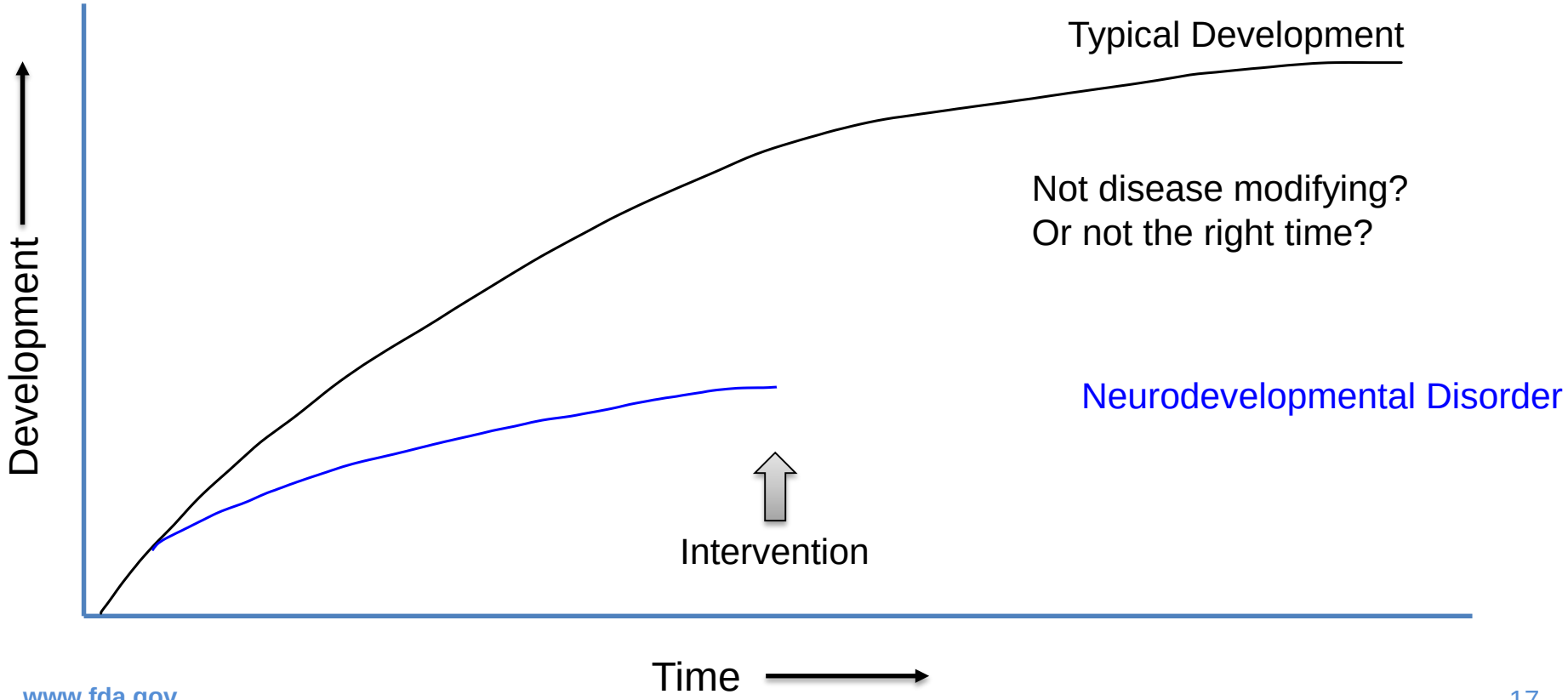

Conclusions

- Approach to disease modification is fairly consistent across review divisions
- In psychiatry, considerations of disease modification are limited by our understanding of pathophysiology
- Observation of a change in syndrome course is insufficient for a disease modification claim
- We propose a framework emphasizing the relationship between disease components and manifestations
- Programs seeking a disease modification claim for treatment of a neurodevelopmental disorder face additional challenges

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