BAYESIAN FRAMEWORKS FOR RARE DISEASE CLINICAL DEVELOPMENT PROGRAMS

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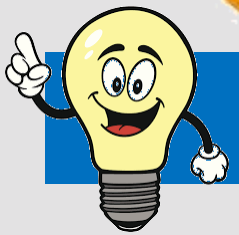
OUTLINE

- Introduction
- Natural history studies
- Long-term safety evaluation and usage of Real-World Data in rare diseases
- Bayesian approaches in rare disease
  - Clinical trial designs
  - Bayesian approaches
- Case study
- Conclusions and future directions

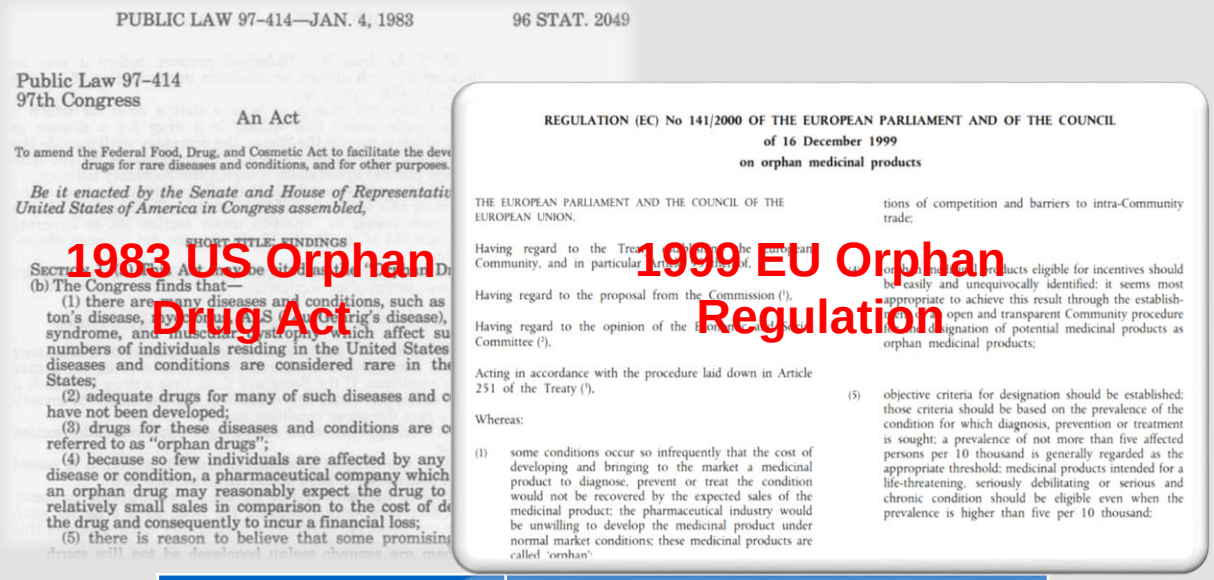
REGULATORY BACKGROUND OF RARE DISEASES

Common Diseases

Rare Diseases



Prevalence



PUBLIC LAW 97-414—JAN. 4, 1983 96 STAT. 2049

Public Law 97-414
97th Congress

An Act

To amend the Federal Food, Drug, and Cosmetic Act to facilitate the deve drugs for rare diseases and conditions, and for other purposes.

Be it enacted by the Senate and House of Representati United States of America in Congress assembled,

SHORT TITLE; FINDINGS

(b) The Congress finds that—
(1) there are many diseases and conditions, such as ton's disease, [illegible] Lou Gehrig's disease), syndrome, and muscular dystrophy which affect su numbers of individuals residing in the United States diseases and conditions are considered rare in the States;
(2) adequate drugs for many of such diseases and c have not been developed;
(3) drugs for these diseases and conditions are c referred to as "orphan drugs";
(4) because so few individuals are affected by any disease or condition, a pharmaceutical company which an orphan drug may reasonably expect the drug to relatively small sales in comparison to the cost of d the drug and consequently to incur a financial loss;
(5) there is reason to believe that some promising

1983 US Orphan Drug Act

REGULATION (EC) No 141/2000 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL
of 16 December 1999
on orphan medicinal products

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty [illegible] Community, and in particular [illegible]

Having regard to the proposal from the Commission (1),

Having regard to the opinion of the Economic and Social Committee (2),

Acting in accordance with the procedure laid down in Article 251 of the Treaty (3),

Whereas:

(1) some conditions occur so infrequently that the cost of developing and bringing to the market a medicinal product to diagnose, prevent or treat the condition would not be recovered by the expected sales of the medicinal product; the pharmaceutical industry would be unwilling to develop the medicinal product under normal market conditions; these medicinal products are called 'orphan';

tions of competition and barriers to intra-Community trade;

[illegible] products eligible for incentives should be easily and unequivocally identified; it seems most appropriate to achieve this result through the establish- [illegible] open and transparent Community procedure [illegible] designation of potential medicinal products as orphan medicinal products;

(5) objective criteria for designation should be established; those criteria should be based on the prevalence of the condition for which diagnosis, prevention or treatment is sought; a prevalence of not more than five affected persons per 10 thousand is generally regarded as the appropriate threshold; medicinal products intended for a life-threatening, seriously debilitating or serious and chronic condition should be eligible even when the prevalence is higher than five per 10 thousand;

1999 EU Orphan Regulation

Country	Threshold
US	< 200,000
EU	< 1/2,000
Japan	< 50,000 ↔ < 4/10,000
Singapore	< 20,000

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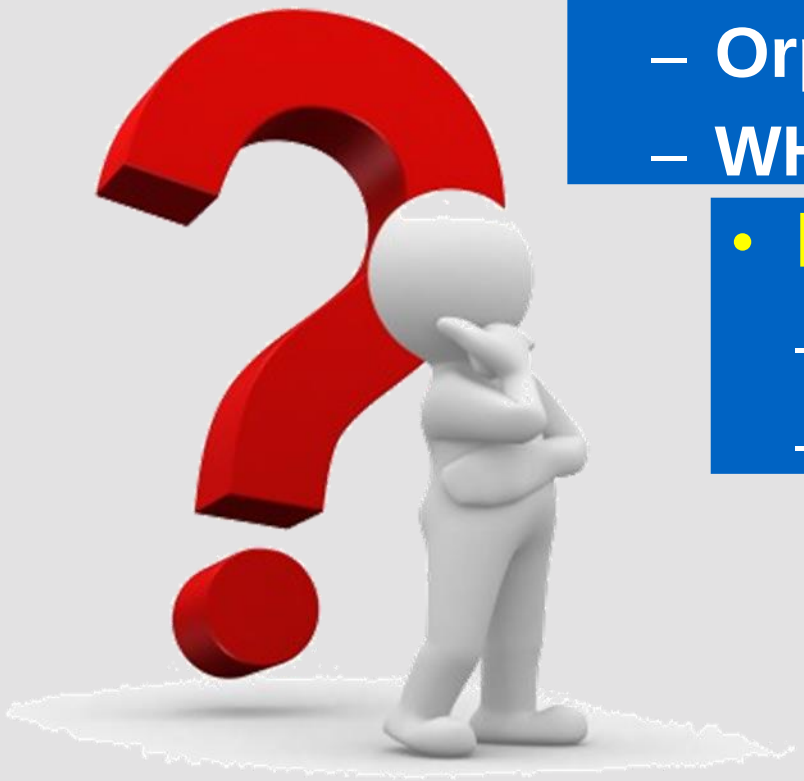
RARE DISEASES FACTS



- **How many rare diseases?**
  - Orphanet: 6,000-7,000
  - WHO: 5,000-8,000
- **How many people have rare diseases?**
  - US: 25-30 million
  - Worldwide: 300-400 million
- **What kind of diseases?**
  - 80% genetic and chronic
- **How old are those patients?**
  - 70% pediatric

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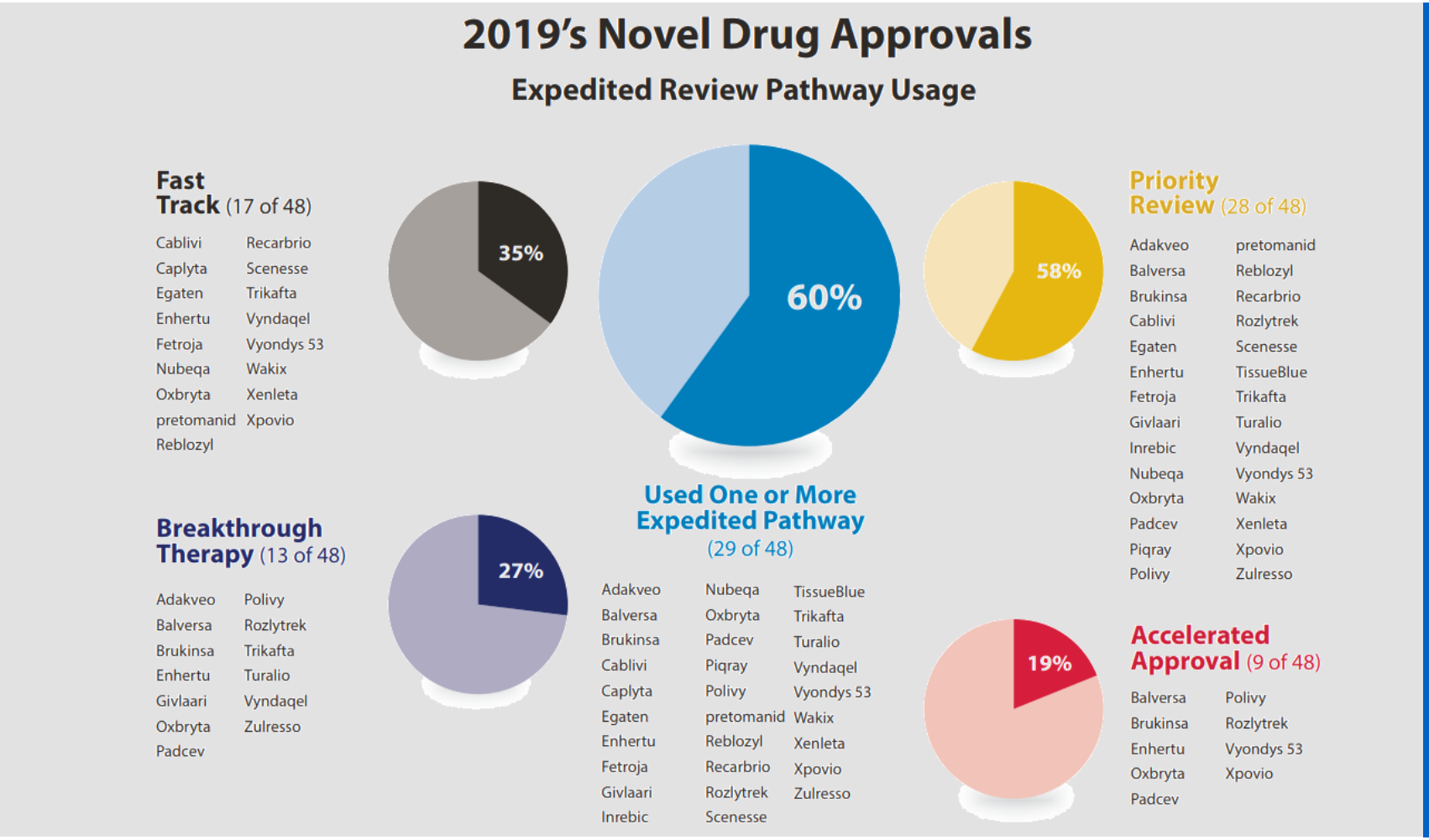
US FDA CDER NEW DRUG APPROVALS (2019)



- Usage of expedited review pathway has been the majority of novel drug approvals
- Priority review consistently comprises the largest percentage

Source: CDER New Drug Therapy Approvals 2019 (https://www.fda.gov/media/134493/download)

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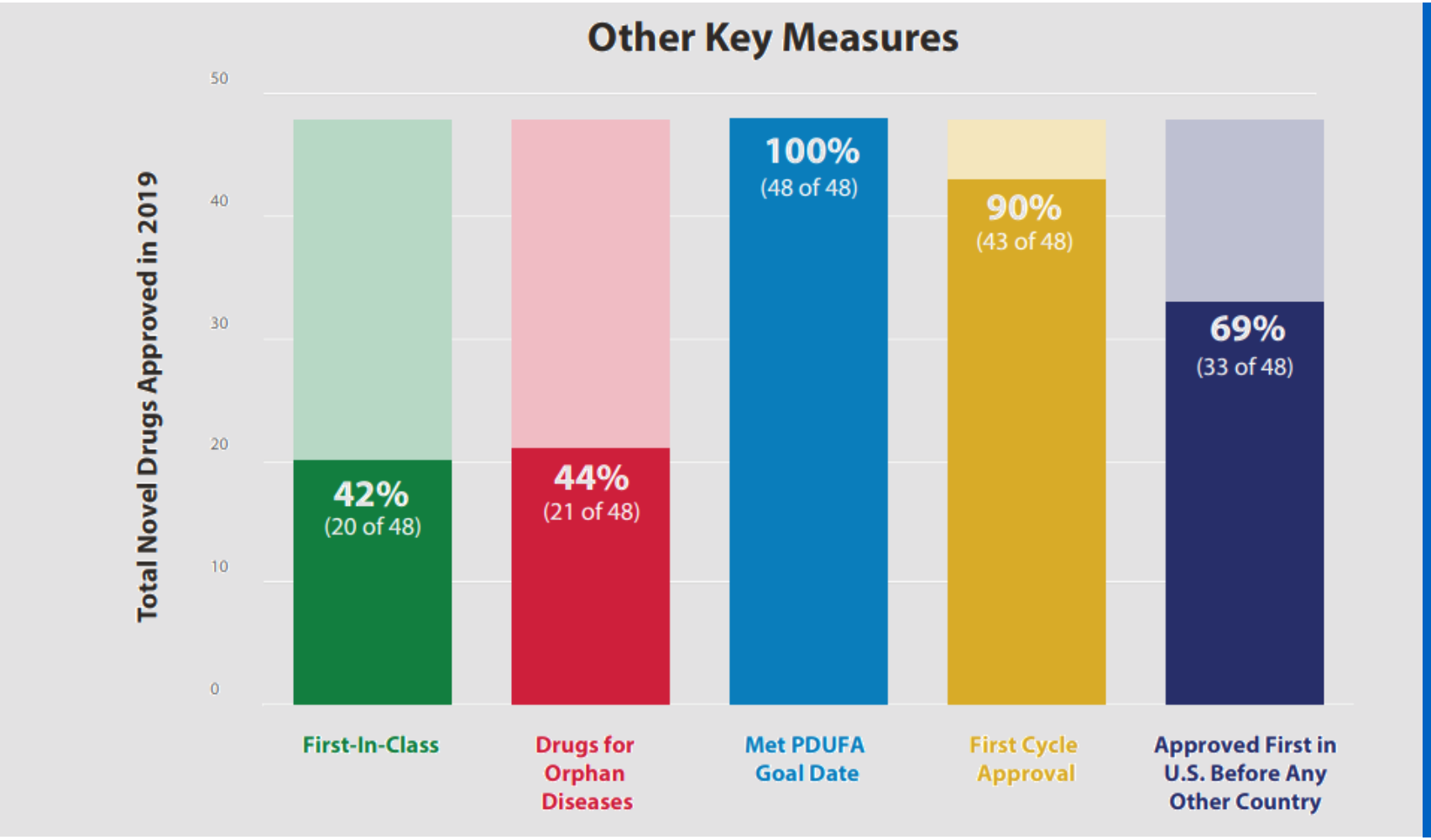
US FDA CDER NEW DRUG APPROVALS (2019) – CONT.



- 30-40% are identified as first-in-class in the past few years
- 44% of approval for orphan disease is lower than 58% in 2018, but higher than 33% and 41% in 2017 and 2016, respectively

Source: Reports & Budgets | CDER – Reports and budgets from CDER offices and divisions (https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/reports-budgets-cder)

NATURAL HISTORY STUDIES

- **Natural History:** Course of development of a disease or condition without treatment
- **FDA Guidance:** Design and conduct natural history studies at the earliest stages of drug development
- **Objectives of Natural History Studies:**
  - Define the disease population
  - Understand and implement critical elements in clinical trial design
  - Select clinical endpoints and develop sensitive and specific outcome measures
  - Identify new or validate existing biomarkers
- **Example:** Myozyme/Lumizyme (alglucosidase alfa) – Pompe disease

Source: Guidance for Industry – Rare Diseases: Common Issues in Drug Development (https://www.fda.gov/media/119757/download) CDER/CBER *Draft Revision 1 Jan 2019*

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LONG-TERM SAFETY EVALUATION AND USAGE OF REAL-WORLD DATA IN RARE DISEASES

- **Post-Market Surveillance:**
  - Further confirm efficacy and its durability (including studies in minority populations)
  - Detect safety signals
  - Observe real-life patient usage of the products
- **Rare Disease Program:**
  - Expedited approval pathway are often adopted
  - Surrogate endpoints are used for initial approval
- **Real-World Data vs. Natural History**

BAYESIAN CLINICAL TRIAL DESIGNS

- **Clinical Development Program:**
  - Pre-clinical studies
  - Clinical studies
  - Post-market studies
- **Trial Aspects:**
  - Dose selection
  - Go/No-go decisions
  - Subgroup identification
  - Adaptation strategies
- **Platform Trial**
  - Multiple investigational treatments
  - A shared control group
- **Other Design Options**
  - Cross-over
  - Single-arm

BAYESIAN APPROACHES LEVERAGING HISTORICAL DATA

- **Two-Step:**

$$p(\theta \mid D_0) \propto L(\theta \mid D_0)p_0(\theta) \longrightarrow p(\theta \mid D) \propto L(\theta \mid D)p(\theta \mid D_0)$$

- **Power Prior:**

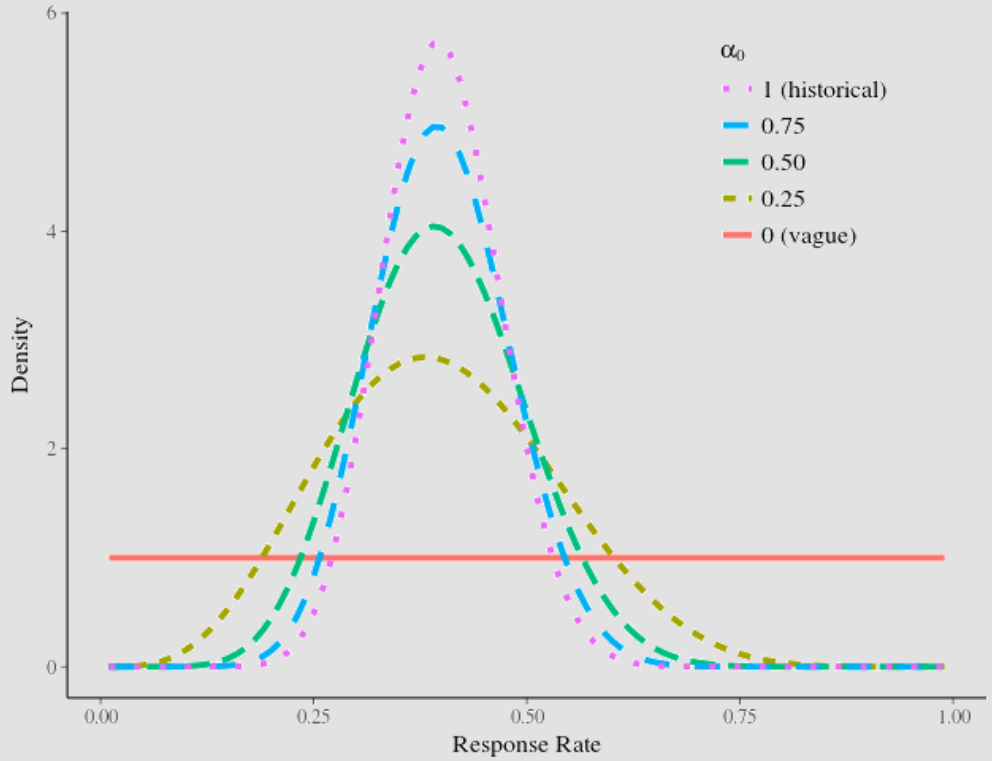
$$p_P(\theta \mid D_0) \propto L\left(\theta \mid D_0\right)^{\alpha_0} p_0(\theta)$$

- **Joint Power Prior:**

$$p_{\mathrm{JPP}}(\theta, \alpha_0 \mid D_0) \propto L\left(\theta \mid D_0\right)^{\alpha_0} p_0(\theta)p(\alpha_0)$$

- **Modified Power Prior:**

$$p_{\mathrm{MPP}}(\theta, \alpha_0 \mid D_0) \propto \frac{L(\theta \mid D_0)^{\alpha_0} p_0(\theta)}{\int L(\theta \mid D_0)^{\alpha_0} p_0(\theta) d\theta} p(\alpha_0)$$



ROBUST MIXTURE PRIOR

$$p_{\mathrm{RMP}}(\theta, w \mid D_0) \propto (1-w)\, p(\theta \mid D_0) + w\, p_r(\theta).$$

$$\Pr(M_r \mid D) = \frac{p(D \mid M_r) w}{p(D \mid M_r) w + p(D \mid M_h)(1-w)}$$

$M_h = p(\theta|D_0)$: Historical data prior

$M_r = p_r(\theta)$: Robust prior (usually weakly informative)

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CASE STUDY

- **Progressive Supranuclear Palsy (PSP):** a rare neurodegenerative disorder characterized by the accumulation of aggregates of tau protein in the brain
- **Prevalence (Orphanet):** 1/16,600* 328.2 mil = 19,771 < 200,000
- **Historical Placebo Data:** Two double-blind, randomized, placebo-control trials (neither met 52-week primary outcome)
  - **Phase II/III:** Davunetide (30 mg) vs. Placebo
  - **Phase II:** Tideglusib (600 and 800 mg) vs. Placebo
- **Primary Endpoint:** PSP-Rating Scale (PSPRS) @ Week 52

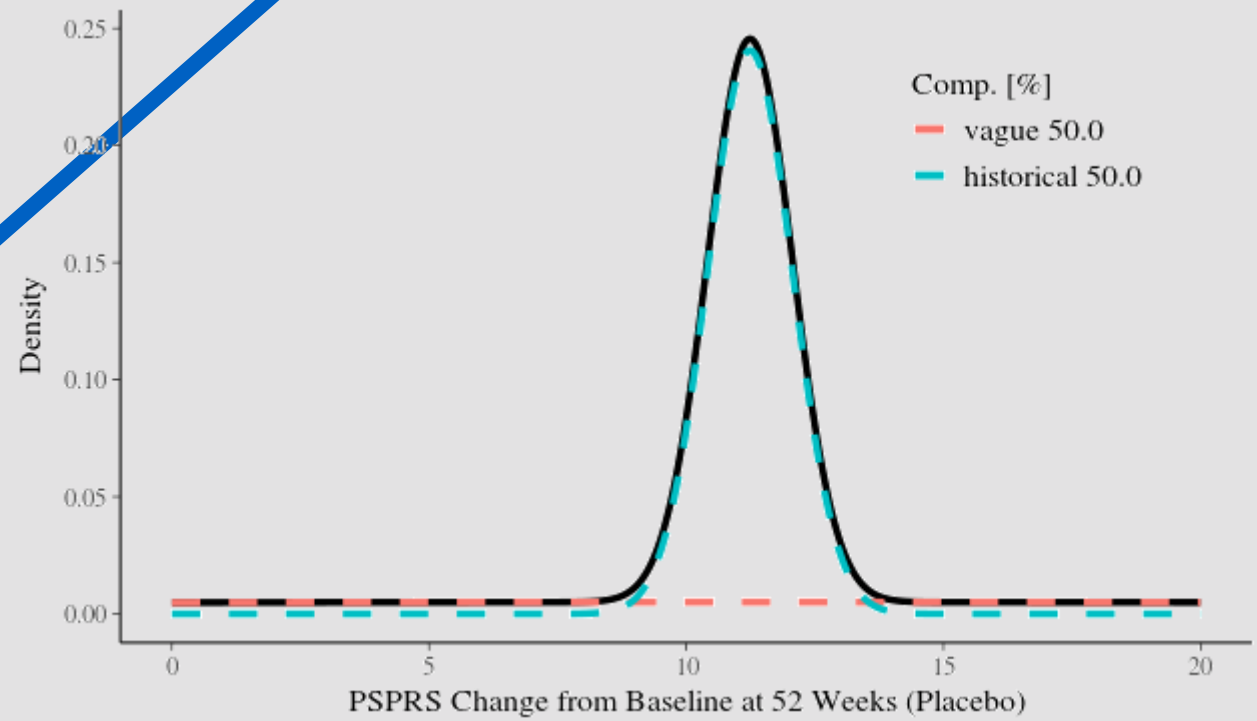
ROBUST MIXTURE PRIOR CONSTRUCTION

$$\theta \mid D_0 \sim \mathrm{N}(\mu = 11.24, \sigma = 9.95/\sqrt{144}),$$

Mean | **Standard Deviation** | **Sample Size**

$$0.5 \times \mathrm{N}(11.24, 9.95/\sqrt{144}) + 0.5 \times \mathrm{N}(11.24, 40)$$

$$\theta_{robust} \sim \mathrm{N}(\mu = 11.24, \sigma = 40)$$

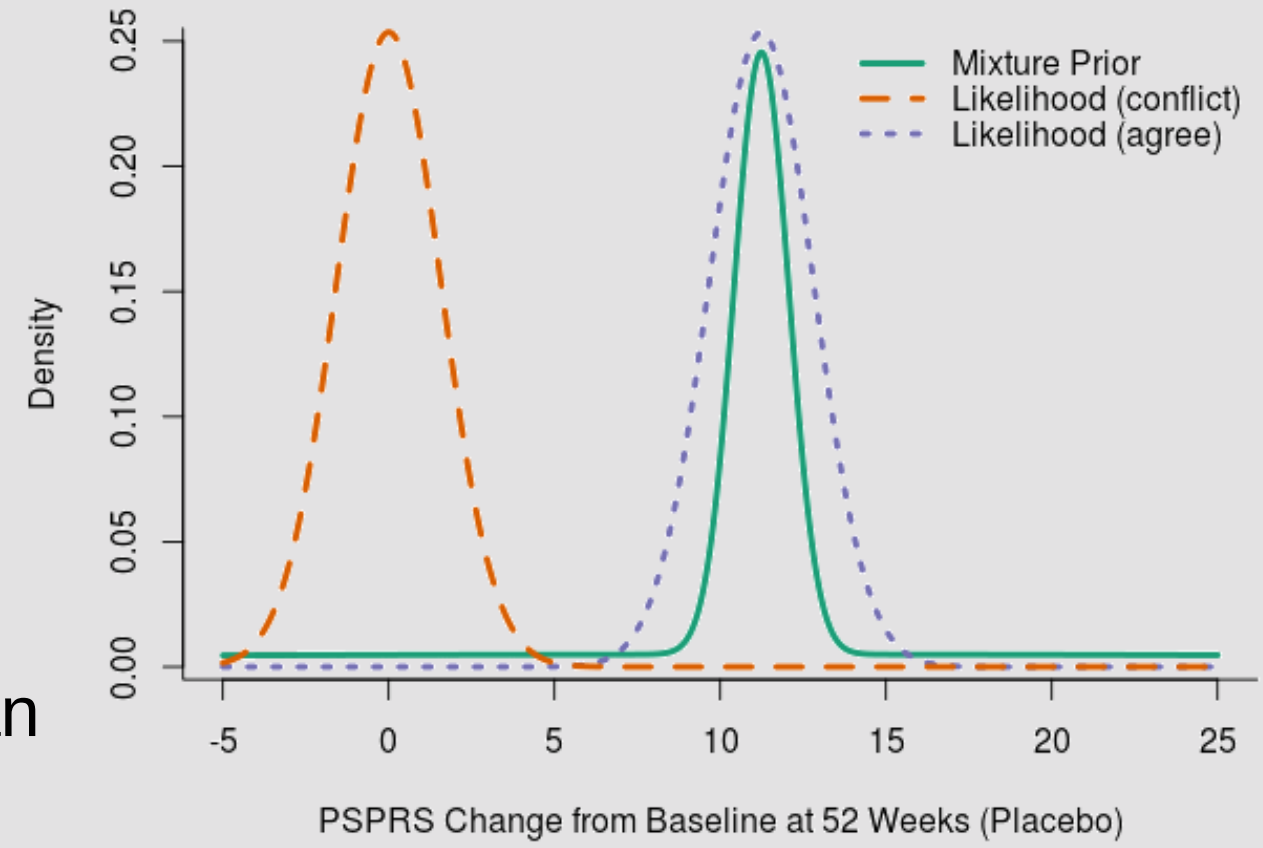


DESIGNING A NEW TRIAL

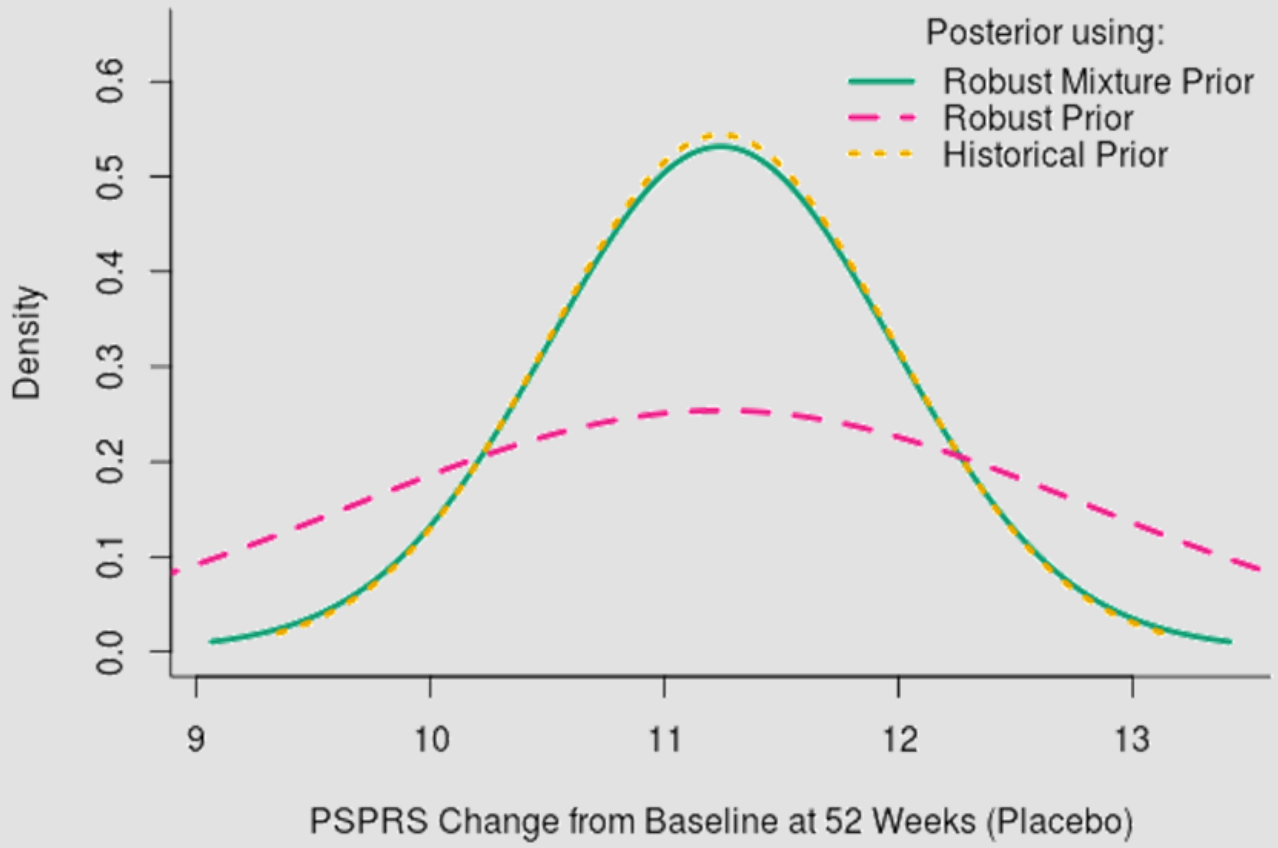
- **N=40 Placebo Patients**
- **Prior-Data Conflict**

  Centered at a mean PSPRS change from baseline at 52 weeks of 0
- **No Prior-Data Conflict**

  Centered at the historical mean of 11.24



POSTERIOR RESULTS (NO PRIOR-DATA CONFLICT)



- Using the robust mixture is nearly equivalent to using the historical prior alone, thus getting the maximal benefit from the historical information
- Using a vague prior, the posterior has much greater uncertainty due to the small sample size

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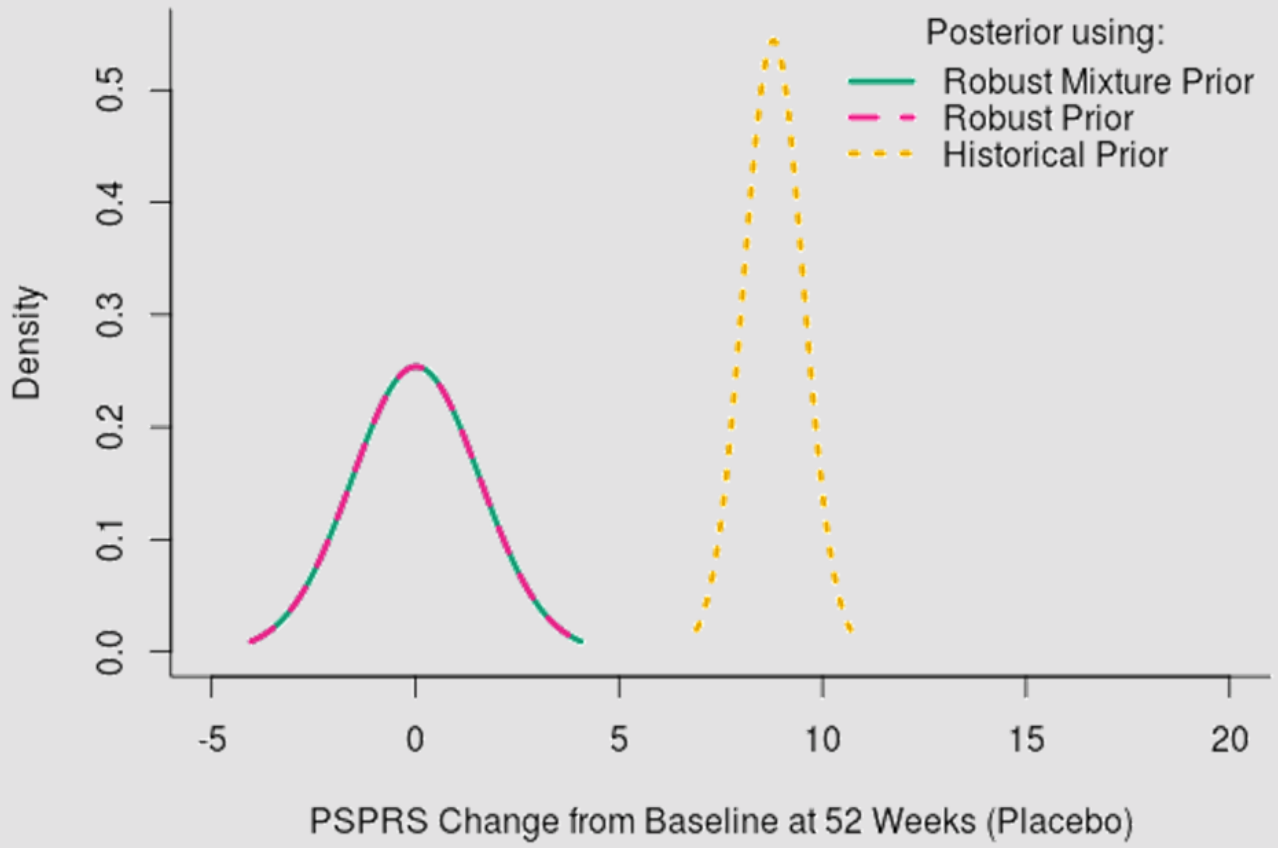
POSTERIOR RESULTS (PRIOR-DATA CONFLICT)



- Using the robust mixture is equivalent to using the robust prior alone
- Using the historical prior, the posterior is actually closer to the historical data due to the small sample size compared to the historical data

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CONCLUSIONS AND FUTURE DIRECTIONS

- **Many current rare disease clinical programs either rely on traditional trial designs with few variations, or are purely based on clinical judgment**
- **The Scottish Medicines Consortium (SMC) has introduced an ultra-orphan definition associated with a new approach to decision-making on such medicines in 2018**
- **US FDA**
  - Requested additional budget for potential ultra-orphan incentives
  - Complex Innovative Trial Design Pilot Program
- **Consider robust Bayesian approaches**

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ACKNOWLEDGEMENT

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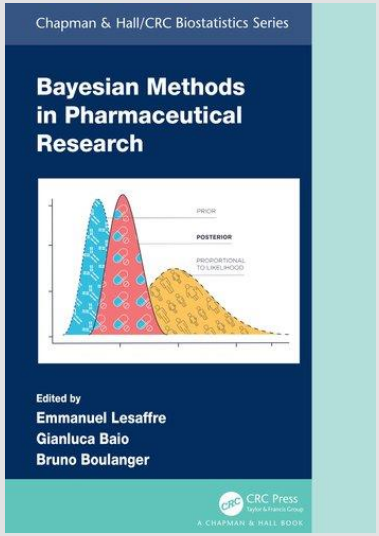

Chapter 12: Bayesian Frameworks for Rare Disease Clinical Development Programs

See also

- Chapter 6: Use of Historical Data
  Beat Neuenschwander and Heinz Schmidli
- Chapter 13: Bayesian Hierarchical Models for Data Extrapolation and Analysis in Pediatric Disease Clinical Trials
  Cynthia Basu and Bradley P. Carlin

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