



# USE OF ENRICHMENT IN DRUG DEVELOPMENT TRIAL DESIGN

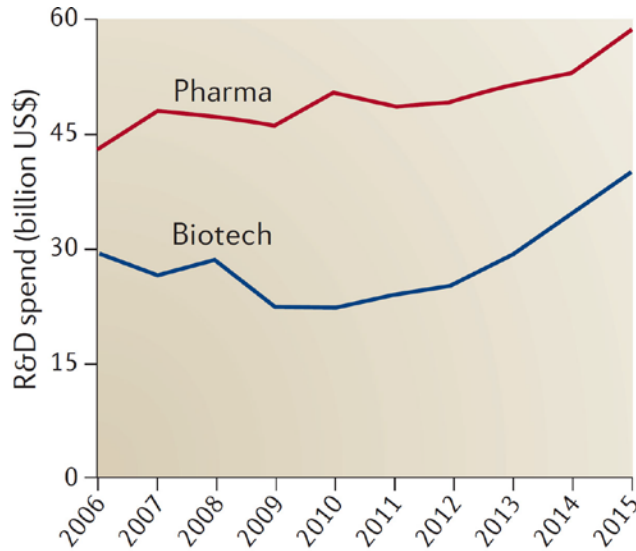
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Office of Translational Sciences | CDER | US FDA

Pediatric Trial Design and Modeling: Moving into the Next Decade | 9.8.2017

# Outline

- **Problem Statement: The Drug Development Landscape**
- **Enrichment in Drug Development: An Overview**
- **Analysis of Pediatric Drug Development**
- **Summary and Conclusions**

# The State of Pharmaceutical R&D



## RESEARCH AND DEVELOPMENT (R&D)<sup>1</sup>

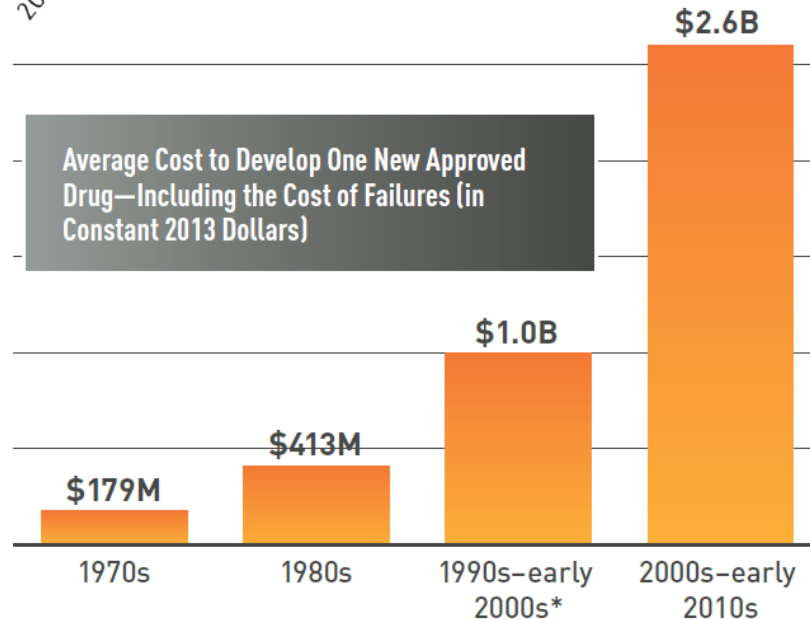
Average time to develop a drug = **10 to 15 years**

Percentage of drugs entering clinical trials resulting in an approved medicine = less than **12%**

### KEY DRIVERS of increasing R&D costs:

- increased clinical trial complexity
- larger clinical trial sizes
- greater focus on targeting chronic and degenerative diseases
- higher failure rates for drugs tested in earlier phase clinical studies

### Average Cost to Develop One New Approved Drug—Including the Cost of Failures (in Constant 2013 Dollars)



# A Case for Optimism

## MEDICINES IN DEVELOPMENT

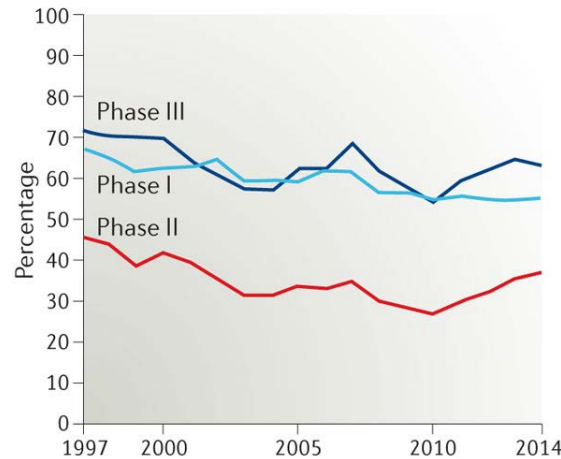
Medicines in development globally = **7,000**<sup>14</sup>

Potential first-in-class medicines\*\* across the pipeline = an average of **70%**<sup>15</sup>

Medicines in development to treat rare diseases = more than **450**<sup>16</sup>

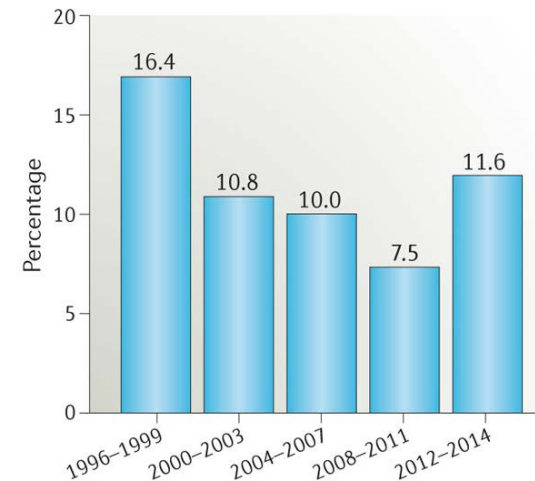
**a Success rates by phase**

Percentage likelihood of moving to next phase, 3-year rolling average\*



**b Cumulative success rate Phase I to launch**

Percentage likelihood of moving from Phase I to launch



1. Improved understanding of disease biology (target selection, patient enrollment, endpoint selection)
2. Better approaches to assessing/assure target engagement, pharmacological activity (POM, POC)
3. Translational safety assessment
4. Increased focus on patient selection (precision medicine, selection biomarkers)
5. Better accounting for sources of variability

# Enrichment

- Prospective use of patient-specific factors to identify a group with increased likelihood for demonstrating drug effect (if one exists)

COMMUN. STATIST.—THEORY METH., 23(2), 499-531 (1994)

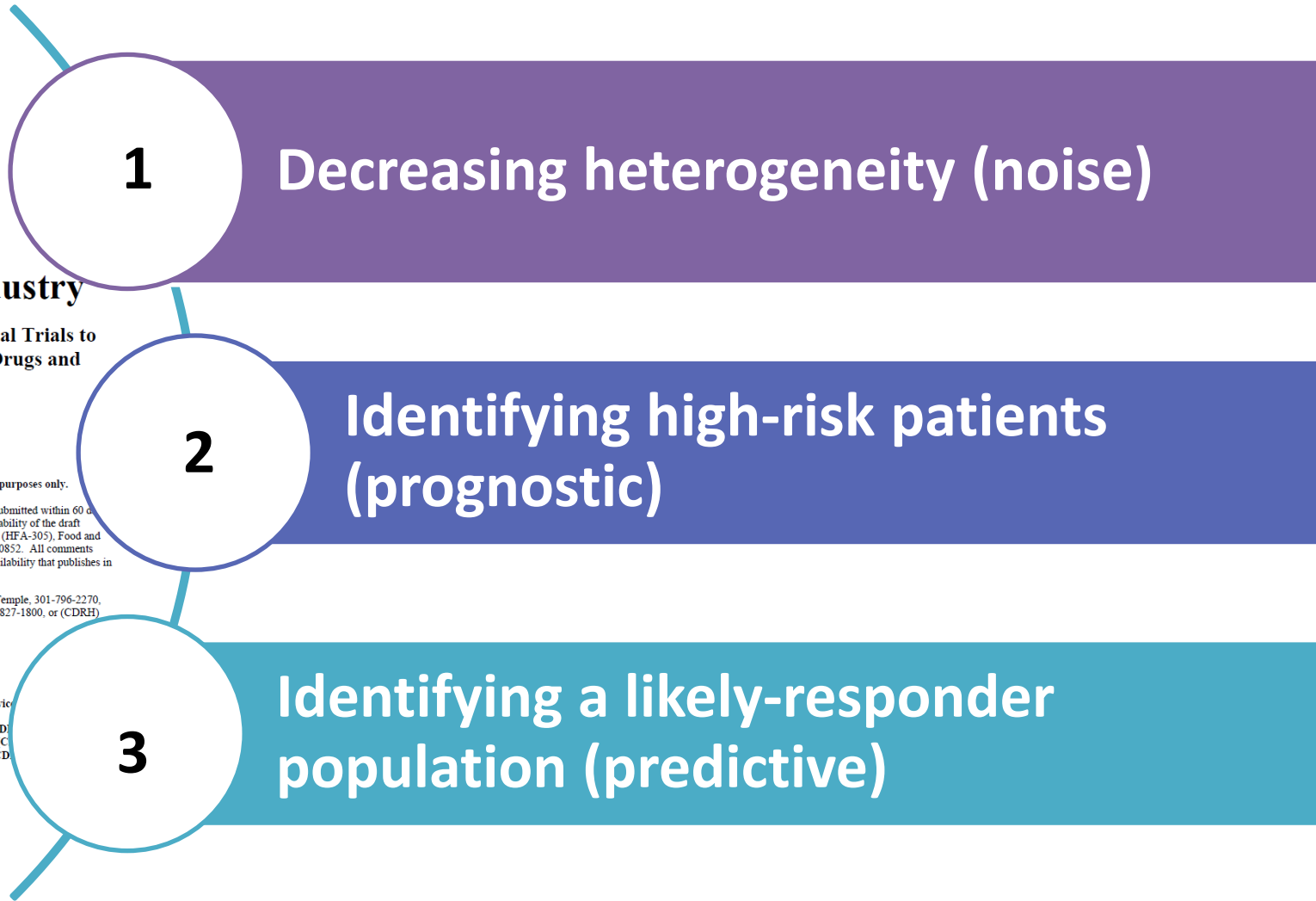
SPECIAL STUDY DESIGNS: EARLY ESCAPE, ENRICHMENT,  
STUDIES IN NON-RESPONDERS

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- Every trial essentially does this by studying a non-random sample of the population

# Enrichment



## Guidance for Industry

### Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products

#### DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Robert Temple, 301-796-2270, (CBER) Office of Communication, Outreach and Development, 301-827-1800, or (CDRH) Robert L. Becker, Jr., 301-796-6211.

U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)  
Center for Biologics Evaluation and Research (CBER)  
Center for Devices and Radiological Health (CDRH)  
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Clinical Medical

# Decreasing Heterogeneity (Non-Drug-Related Variability)



- Defining entry criteria carefully, training investigators to ensure enrolled patients have the disease of interest
- Identifying and selecting patients likely to comply with treatment (↓ variability in drug exposure)
  - Making patients aware of the conditions/demands of the trial, avoiding too-rapid titration, using adherence prompts, alert systems, and “pill counting”/smart bottles
- Eliminate spontaneous improvers or placebo responders
  - Placebo-lead in prior to randomization
- Enrolling only patients who give consistent baseline values (↓ intra-patient variability)
- Excluding patients taking drugs that are pharmacologically similar to, or that could interact with, the study drug

# Prognostic Enrichment

- Enroll patients with some baseline feature(s) that associate with higher likelihood of events of interest
  - Medical/family history
  - Clinical/lab measures
  - “Omic” biomarkers
- Increases absolute effect size
- Primary and secondary prevention trials
- Disease modification (delayed progression) trials
- Commonly employed
  - Start with high-risk (e.g., secondary prevention, metastatic disease) and move to lower risk



# Predictive Enrichment

- Study patients with higher likelihood for response
  - Increased efficiency (caveat: screening)
  - Potential for enhanced B/R balance
- Empiric strategies: based on observations during screening or prior experience with drug/related drugs
  - Does not rely on understanding basis for response variability
  - Open trial period followed by randomization of responders
  - Randomized withdrawal design
  - Studies in non-responders or patients intolerant to other therapy
- Pathophysiologic (including genomic) strategies: mostly refers to baseline germline, somatic, or circulating biomarker, but can also include PD biomarker
  - Targeted therapies
  - “Precision medicine”

# Enrichment: General Considerations



- Performance characteristics of the screening strategy
- Timing of biomarker (classifier) development
- Studying of EF+ only patients (vis-à-vis some EF-)
- Multiplicity (type 1 error rate control)
- Adaptive enrichment
- Interpretation
- Labeling

# Enrichment: General Considerations



- Performance characteristics of the screening strategy
  - Less well known/studied prognostic or predictive EFs can have profoundly adverse impact on the clinical trial if poorly sensitive (over exclusive) or poorly specific (over inclusive)
  - Performance and ease of measurement important if to be used in clinic
- Timing of biomarker (classifier) development
  - Depends on priors (e.g., strength of mechanistic hypothesis/evidence, empirical data on response in subgroups)
- Studying of EF+ only patients (vis-à-vis some EF-)
  - Depends on likelihood for effect in EF- and ability to assess EF prior to randomization
  - Restricted entry, stratified randomization, hierarchical testing<sub>1</sub>

# Enrichment: General Considerations



- Labeling
  - Use of enrichment designs will often have implications for labeling (Indications; Usage; Dosage and Administration; Clinical Studies sections)
  - Prognostic enrichment will be described in Clinical Studies and has sometimes led to a description of the studied population in Indications
  - Predictive enrichment will usually lead to an indication directed at the predictive enrichment population, often with recommended testing, and a description of the selection in Clinical Studies
  - Whether the EF- group was studied, what (if any) response was observed in that subset, and whether or not significant toxicity exists for the drug overall would all influence labeling in terms of language around which patients could receive treatment
  - An IVD may be necessary

# Outline

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# Enrichment in Pediatric Drug Development: Analysis of Trials Submitted to the US FDA



- Enrichment may be particularly valuable when: 1) limited number of patients; 2) when there have been difficulties in achieving successful clinical trials
- Both are true in pediatrics, resulting in trial difficulties and inability to approve the drug for pediatric use
- Optimizing enrichment strategies for pediatric trials appears to be a reasonable approach to increase trial success rates (e.g., migraine, neurogenic bladder)
- A systematic evaluation of enrichment strategy approaches in pediatric drug development trials has not been performed to date
- **ACKNOWLEDGMENT: Dionna Green, Xiaomei Liu, Janelle Burnham, Gilbert Burckart**

## Methods

- Pediatric efficacy trials from drug development programs submitted to FDA (2012 – 2016)
- Enrichment strategies were categorized broadly as practical, prognostic, or predictive
- Trial outcome was categorized as a success or failure based upon whether or not the trial successfully met its primary efficacy endpoint
- Program outcome was categorized as successful/failed based upon whether the pivotal trial(s) resulted in FDA approval for use in the pediatric population studied

# Summary and Conclusions

- In general, R&D costs (\$, time, and opportunity) remain high
- Efficiency (early attrition, late success) is showing signs of improvement, likely (at least in part) due to advances in clinical and translational science
- These advances can lead to more informed clinical trials, e.g., through use of enrichment strategies
- Enrichment has been an area of much interest to FDA and drug development for decades
- Enrichment strategies are widely used in pediatric drug development (at the trial level)
- Data suggest that pediatric trials are more likely to succeed with enrichment strategies are employed



