Paediatric Medicines Development
The Need for Different Approaches

EMA Workshop on Extrapolation

European Medicines Agency
London, UK

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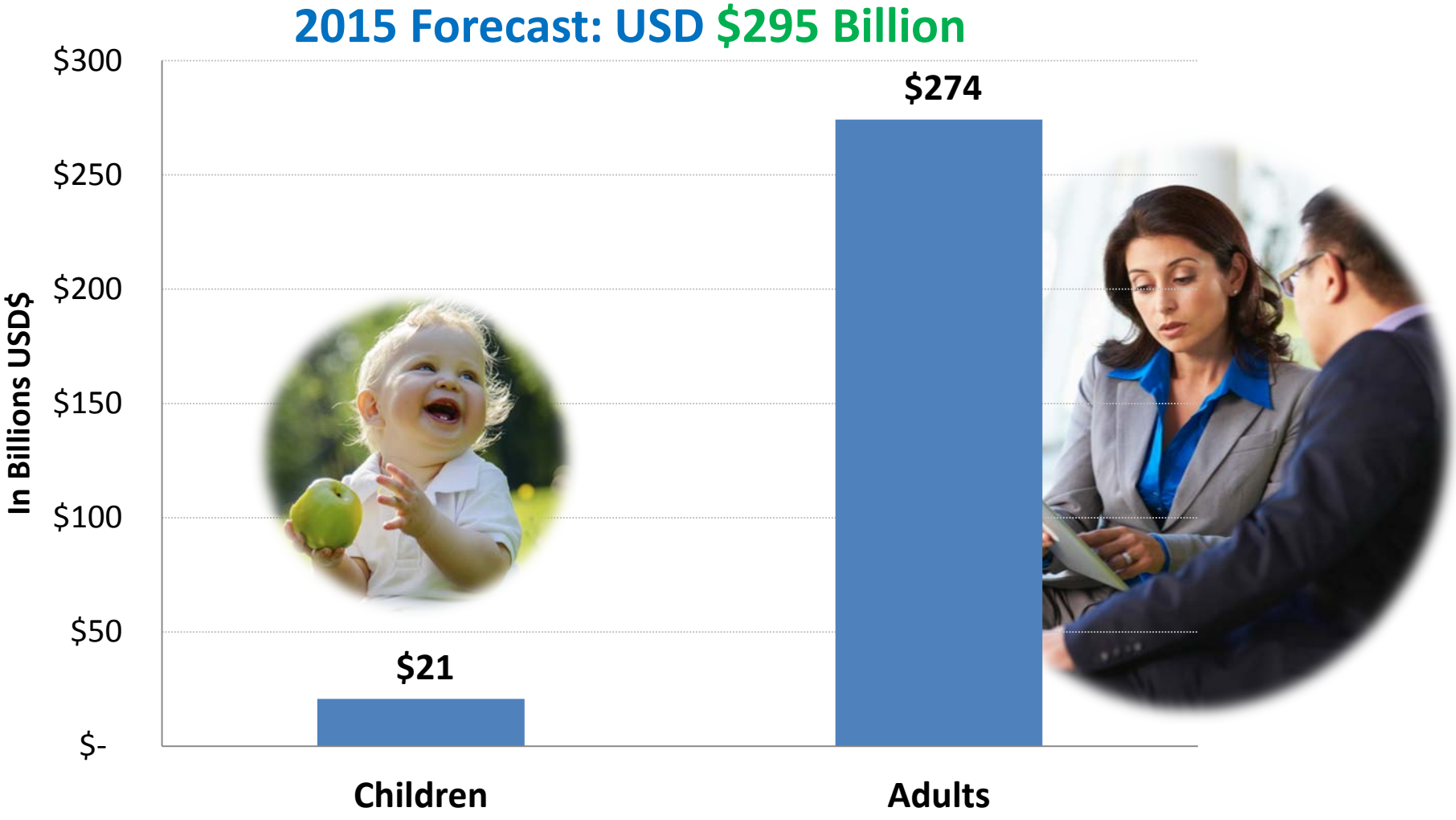
Challenges we face

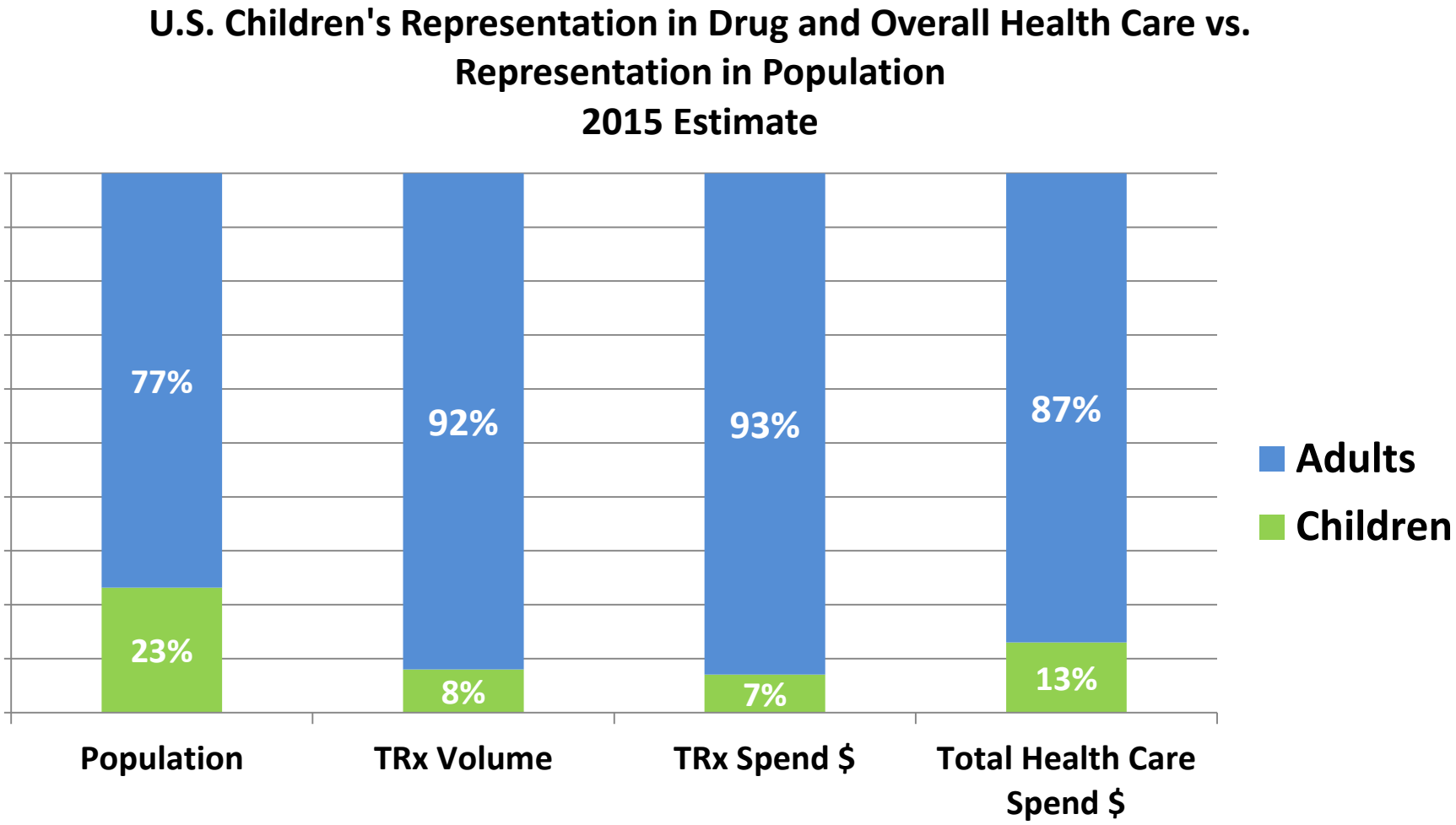
Size

U.S. Prescription Drug Purchases (Retail) Children vs. Adults



Source: CMS.gov. National Health Expenditure Data. Age & Gender. Accessed July 2015.

U.S. Children's Portion of Health Care



As a Society, We Have Work to Do...

Over

60%

of medicines used to treat children have not been studied in children.

Over

90%

of them have not been studied in infants.

Complexity

Different Doses, Different Formulations

Small Populations and Sub-Populations

At least Five Paediatric Sub-Populations

Preterm Newborn Infants	Term Newborn Infants	Infants and Toddlers	Children	Adolescents
Pre-term	*0–28 days*	*29 days to 23 months*	*2 Years to 11 Years*	*12 Years to 18 Years*

- Incidence of most diseases in children is relatively low
- Conducting studies requires segmentation into five or more pediatric sub-populations
- Eligibility criteria further narrow the pool eligible to be enrolled in a study
- For each sub-population, separate clinical studies are often required

**There are several definitions and demarcations for the pediatric subpopulations; this is only one example. Illustrates the need to stratify the population.*

Paediatric Trial With the Same Anti-hypertensive

Adult

- N = 220 subjects
- Countries: One (USA)
- No. Sites: 9
- Study time: 5 months
- 24 subjects per site

Paediatrics (6-16 y/o)

- N = 253 subjects
- Countries: Three
- No. Sites: 70
- Study time: 1 year
- 3 – 5 subjects per site

Thank you to Dr. Ron Portman for providing this example

Opportunities for Efficiency

Efficiency lowers R&D investment and increases likelihood of success

1

Site Selection & Throughput

2-5 Patients Per Site over 1-2 Years

2

Aligning CDA, Contracts and have a single ICF

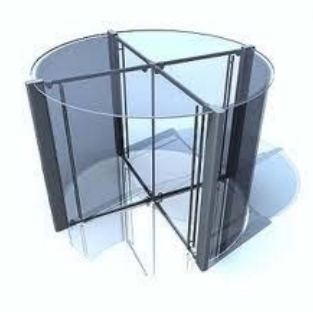
3

Minimize Protocol Amendments

9 amendments slowed enrollment

4

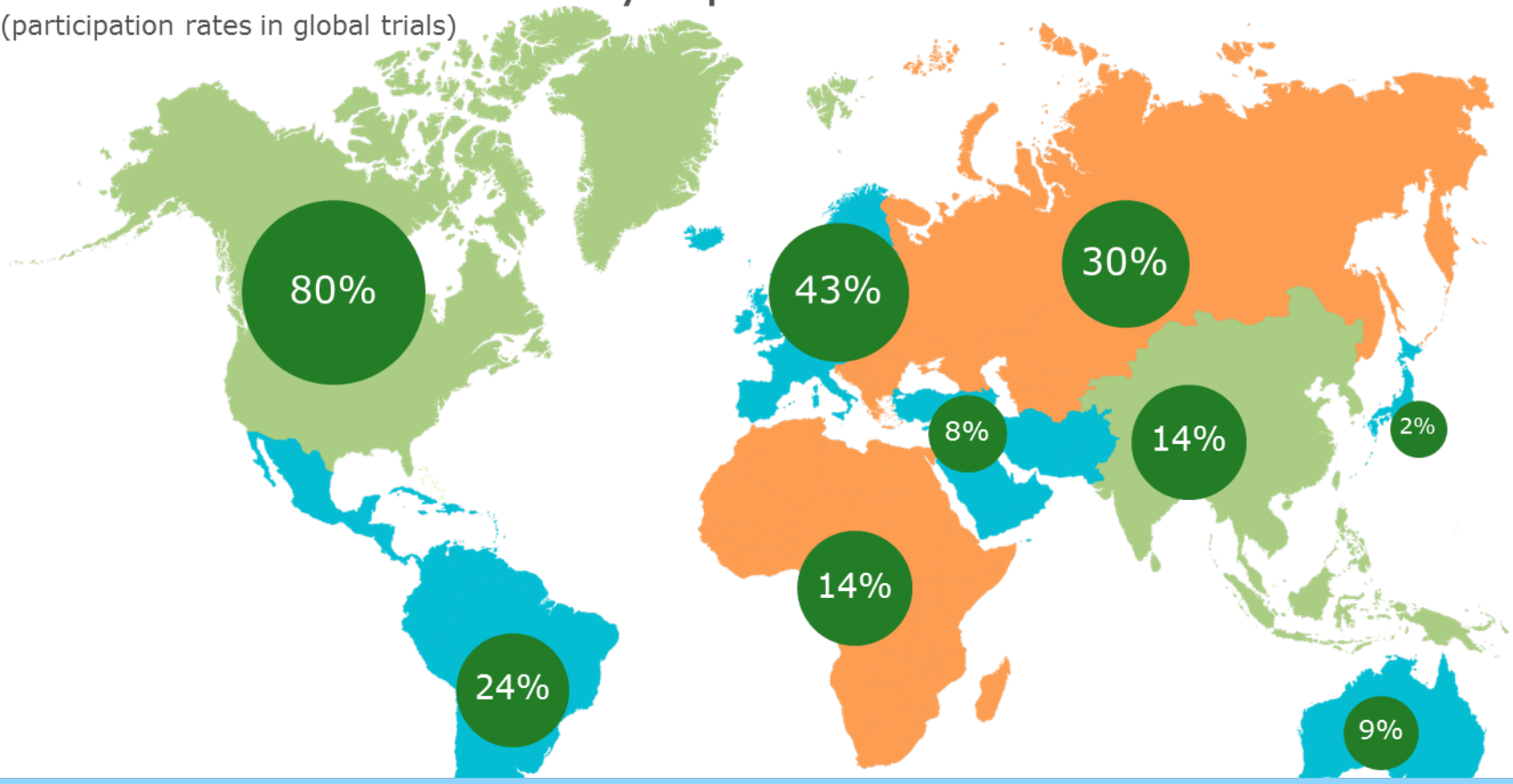
Staffing Consistency



Global Outreach – Low Per Site Participation

Global Pediatric Industry-Sponsored Trials

(participation rates in global trials)



30% of sites do not enroll (NA and EU)*

< 1.1 patients per site per year**

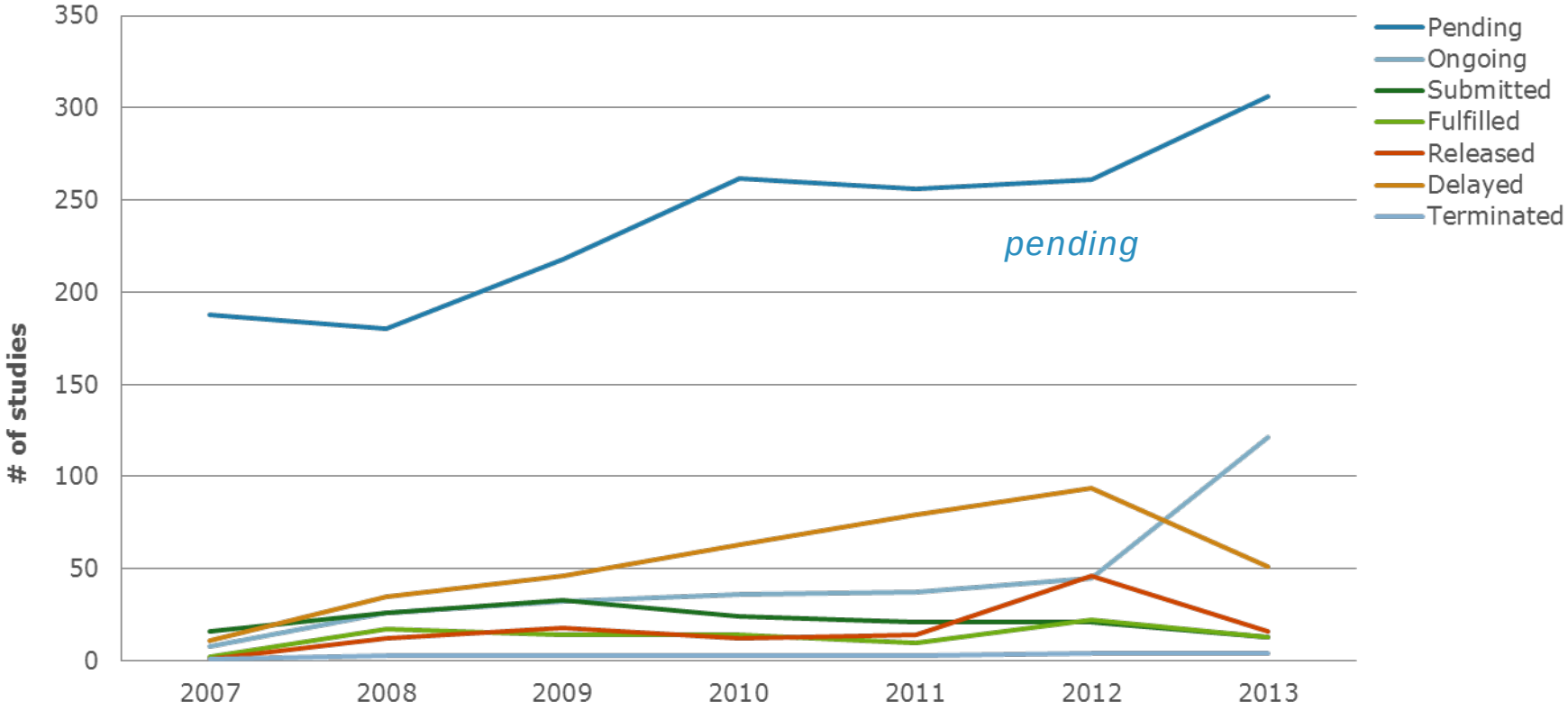
*Sources: *Janssen commissioned study – KMR data set, 2013.*
***Medidata random sample, 20 studies, 2012 to 2015*

Industry-Sponsored Trials are Struggling

Annual Snap Shot at Year End
~60% Have Not Yet Enrolled Patients

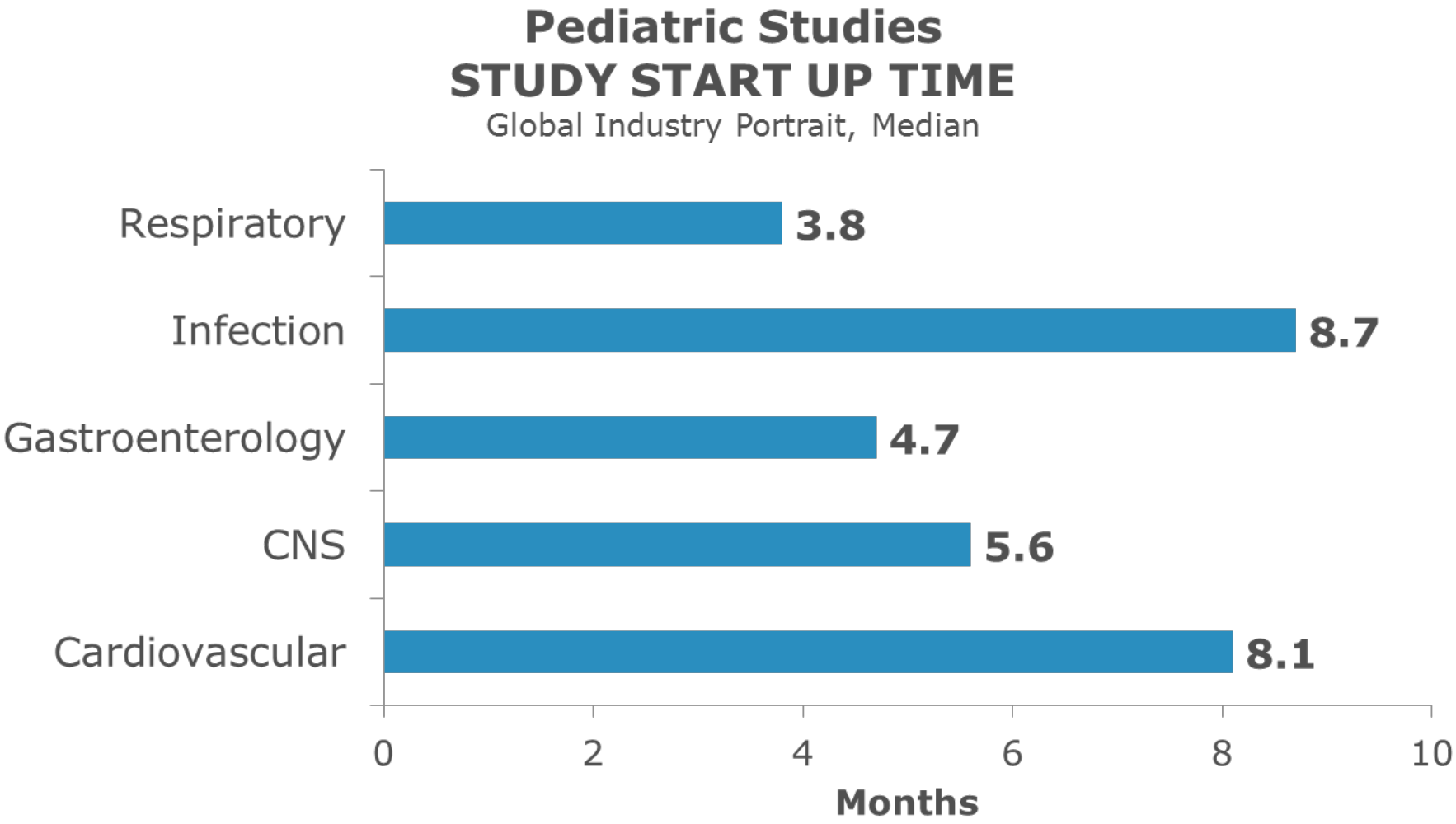
United States

FDA Data Base Accessed September 2014



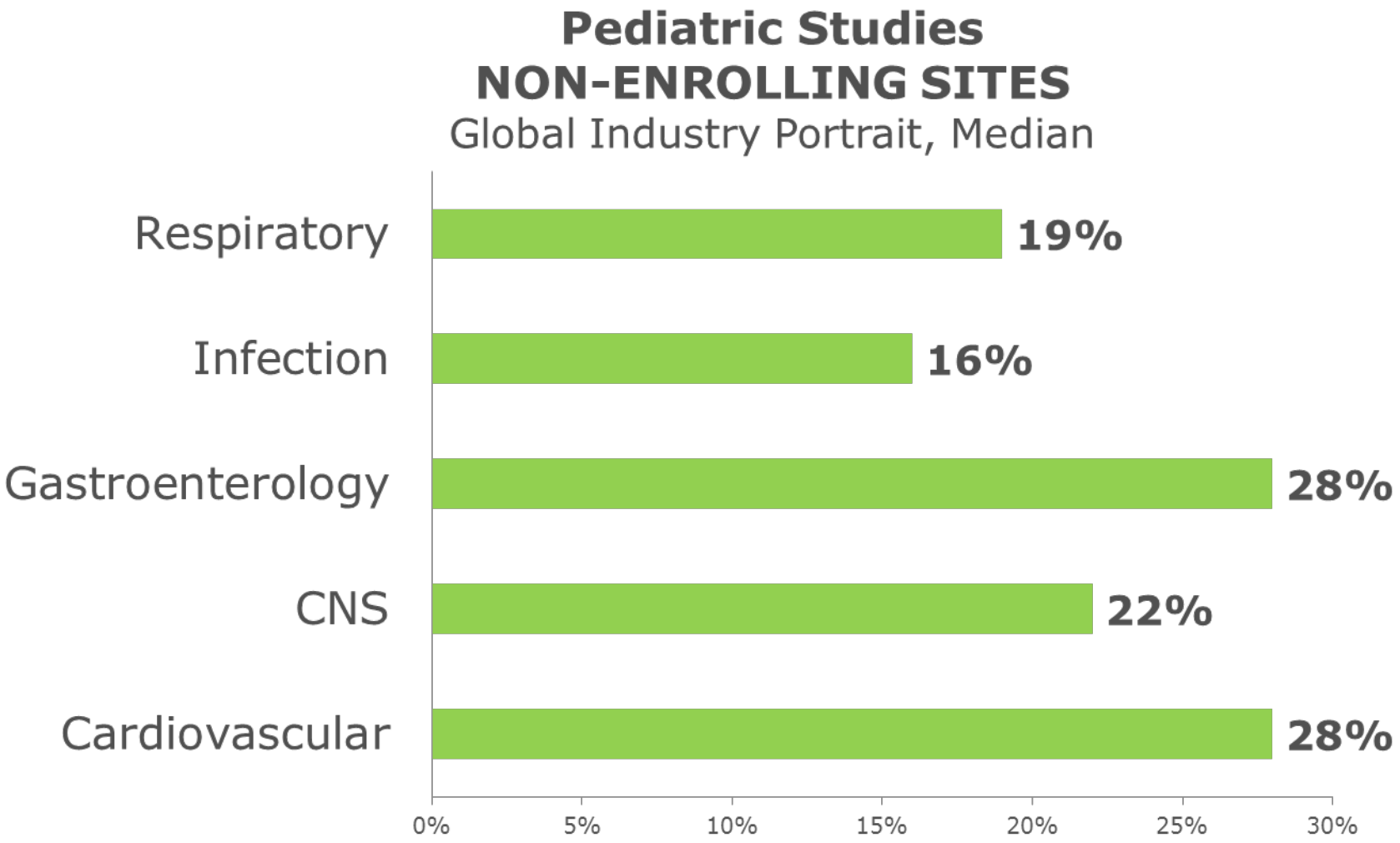
Source: FDA Website Pediatric Studies – Annual Status Summary

Start Up is Very Long



Source: KMR, 2014. n = 135 pediatric industry-sponsored trials, 2009-2013.. Start up time = Protocol approval to FPI.

of Non-Enrolling Sites is Very High



Source: KMR, 2014. n = 135 pediatric industry-sponsored trials, 2009-2013. Non-enrolling = 0 patients enrolled.

Discussion Only

Developing a Clinical Trials Infrastructure in the United States

Paul Eisenberg, Amgen, Inc.; Petra Kaufmann, National Institute of Neurological Disorders and Stroke; Ellen Sigal, Friends of Cancer Research; and Janet Woodcock, U.S. Food and Drug Administration*

April 13, 2012

**Participants in the activities of the IOM Forum on Drug Discovery, Development, and Translation*

Culture Change

"The Pink Sheet"
PRESCRIPTION PHARMACEUTICALS & BIOTECHNOLOGY

FDA's Woodcock Prioritizes Trial Networks As Drug Development Solution

By Sarah Karlin / Email the Author / View Full Issue
Word Count: 1053 / Article # 14140506006 / Posted: May 7 2014 1:10 AM

Executive Summary
Culture change, not congressional action is needed advance this step toward faster drug development, FDA's drug leader tells Energy & Commerce Committee.

The Need of Different Approaches

Alternative ways & tools to develop medicines for children

- Learn how ontogeny affects pharmacotherapy and vice versa
  - Drug metabolizing enzymes
  - Maturation of drug receptors (targets of therapy)
  - Are receptors in children and adults the same in quantity and quality?
- Development and Maturation
  - How maturation affects pharmacological response
  - Develop alternative and measurable clinical endpoints
  - Find clinically relevant biomarkers
  - Use of Modeling and Simulation, Population PK, and other techniques

Paediatric Medicines Development

It is truly in its infancy

EU law is less than **a decade old**

All Beginnings Are Difficult

The Belief

Heart Surgery Has Reached the Limit

"Surgery of the heart has probably reached the limit set by nature to all surgery. **No new method and no new discovery can overcome the natural difficulties that attend a wound of the heart."**

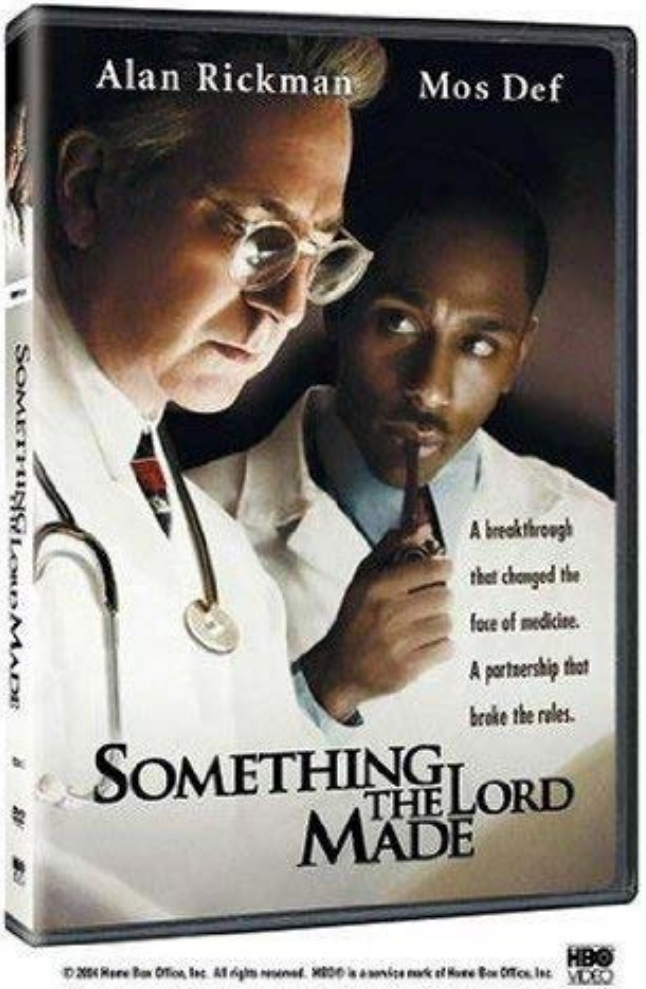
—Stephen Paget, British physician

The Breakthrough
Heart Surgery is Commonplace

“In an era that no longer considers heart transplants miraculous and in which coronary bypass operations are commonplace, it is perhaps difficult to imagine how daring the concept of cardiac surgery once seemed.”

—Mike Field, on the 50th anniversary of the first Blalock-Taussig surgery

The Gazette
The newspaper of The Johns Hopkins University



The Belief

Surgery is the Only Treatment for Cancer

"In treating of cancer, we shall remark, that little or no confidence should be placed either in internal... remedies, and that

there is nothing, except the total separation of the part affected."

—A Dictionary of Practical Surgery, 1836

Leukemia

The most common cancer in children

Leukemia

The most common cancer in children

- Disseminated disease
  - **No surgery will eradicate leukemia**
- Mortality was 100%

The Breakthrough

Sidney Farber

He challenged conventional wisdom and started to experiment with chemotherapy

The Breakthrough

Sidney Farber

He challenged conventional wisdom and started to experiment with chemotherapy

He kept going because his “passion” for a cure was greater than the obstacles facing him

Let Us Change the World!

- Two paediatric conditions believed to be impossible to treat.
- Two paediatric teams that did not accept the belief and faced the challenge to change it.

Forever opened Cardiac Surgery and Oncologic Chemotherapy not only for Children but for the entire world

We can and should do the same for the development of Medicines for children and adults!

Thank You

“Not everything that is faced can be changed, but nothing can be changed until it is faced.”

— **James Baldwin**