



International Neonatal Consortium

The International Neonatal Consortium

Lynn Hudson – Executive Director
Jonathan Davis, Ron Portman, Mark Turner – Co-Directors

May 1 – 3, 2019



1:00 p.m. – 1:05 p.m. Welcome - Joseph Scheeren, President and CEO, Critical Path Institute

1:05 - 1:15 p.m. INC at Four Years: Neonatal Growth and Predicted Long-Term Outcomes

SUSAN MCCUNE, DIRECTOR, OFFICE OF PEDIATRIC THERAPEUTICS, FDA

1:15 p.m. – 2:30 p.m. *Educating the Neonatology Community on the Drug Development Process*, RON PORTMAN

Session I: Setting the Scene, Gerri Baer (OC/FDA), Chair

- Panel: Robert Ward (U-Utah), Susan McCune (OC/FDA), Laura Fabbri (Chiesi)

2:30 p.m. – 3:00 p.m. Coffee Break

3:00 p.m. – 4:25p.m.

Session II: Harnessing the Science, Christina Bucci-Rechtweg (Novartis), Chair

- PANEL: NORMAN BARTON (Takeda), CHRIS MILNE (Tufts CSDD), THOMAS MILLER (BAYER)

4:25 p.m. – 5:30 p.m.

Session III: Addressing Neonatal Needs within the Current Environment, ED CONNOR (I-ACT for Children), CHAIR

- PANEL: SUSAN MCCUNE (OC/FDA), AGNES KLEIN (HEALTH CANADA), APRILE PILON (Trove Therapeutics), MARY SHORT (LILLY), MARK TURNER (U-LIVERPOOL), JENNIFER DEGL (SPEAKING FOR MOMS AND BABIES, INC.), ANNE ZAJICEK (NIH/OD), KELLE MOLEY (MARCH OF DIMES), JAMES BAUMBERGER (AAP)



International Neonatal Consortium

INC at Four Years: Neonatal Growth and Predicted Long-Term Outcomes

*Susan McCune, M.D.
Director, Office of Pediatric Therapeutics
Office of the Commissioner, FDA*

*International Neonatal Consortium
Introduction
May 1, 2019*

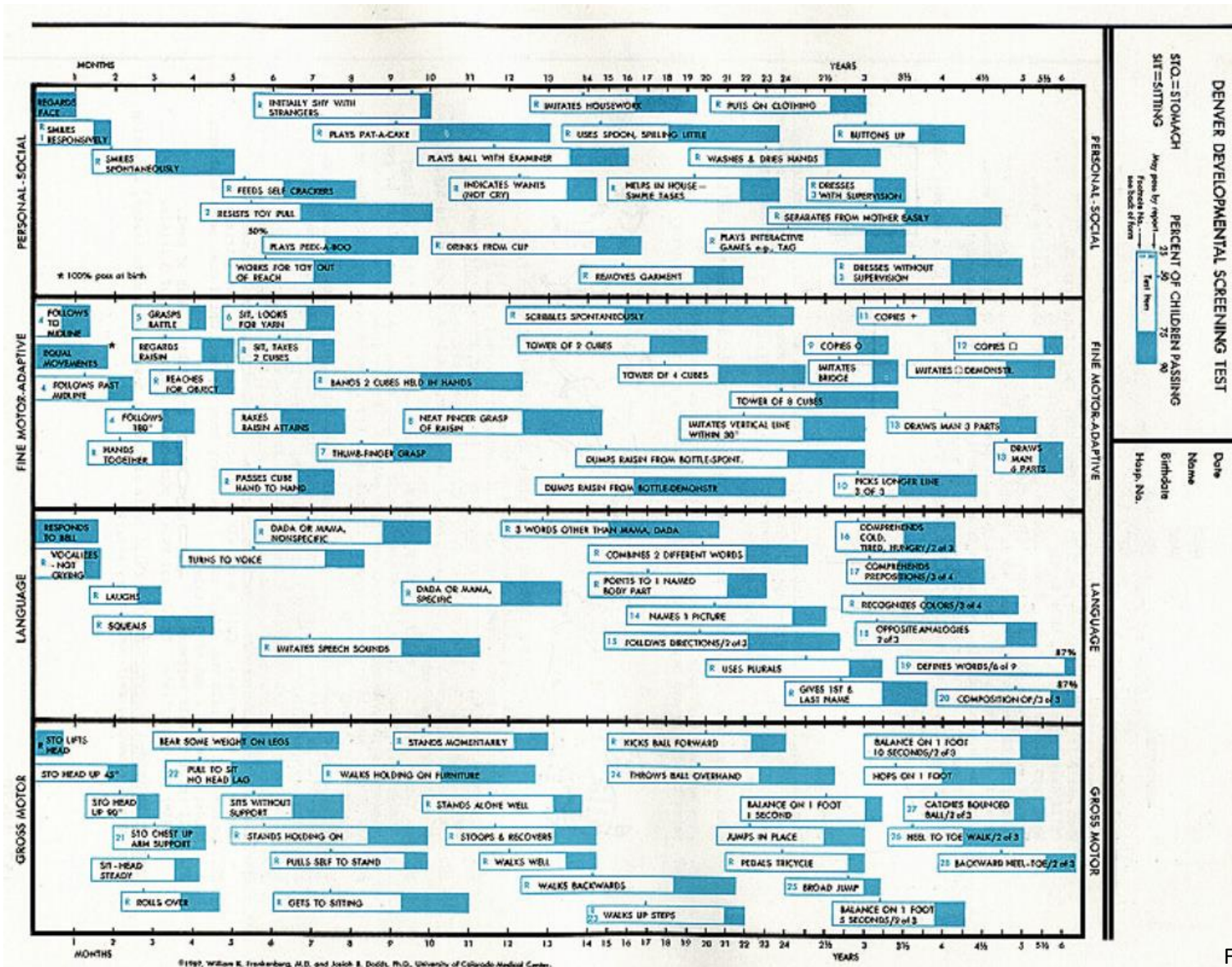


Disclaimer

- The views presented here are personal and do not necessarily reflect the views of the Agency
- All specific drug development questions should be discussed with the relevant review division

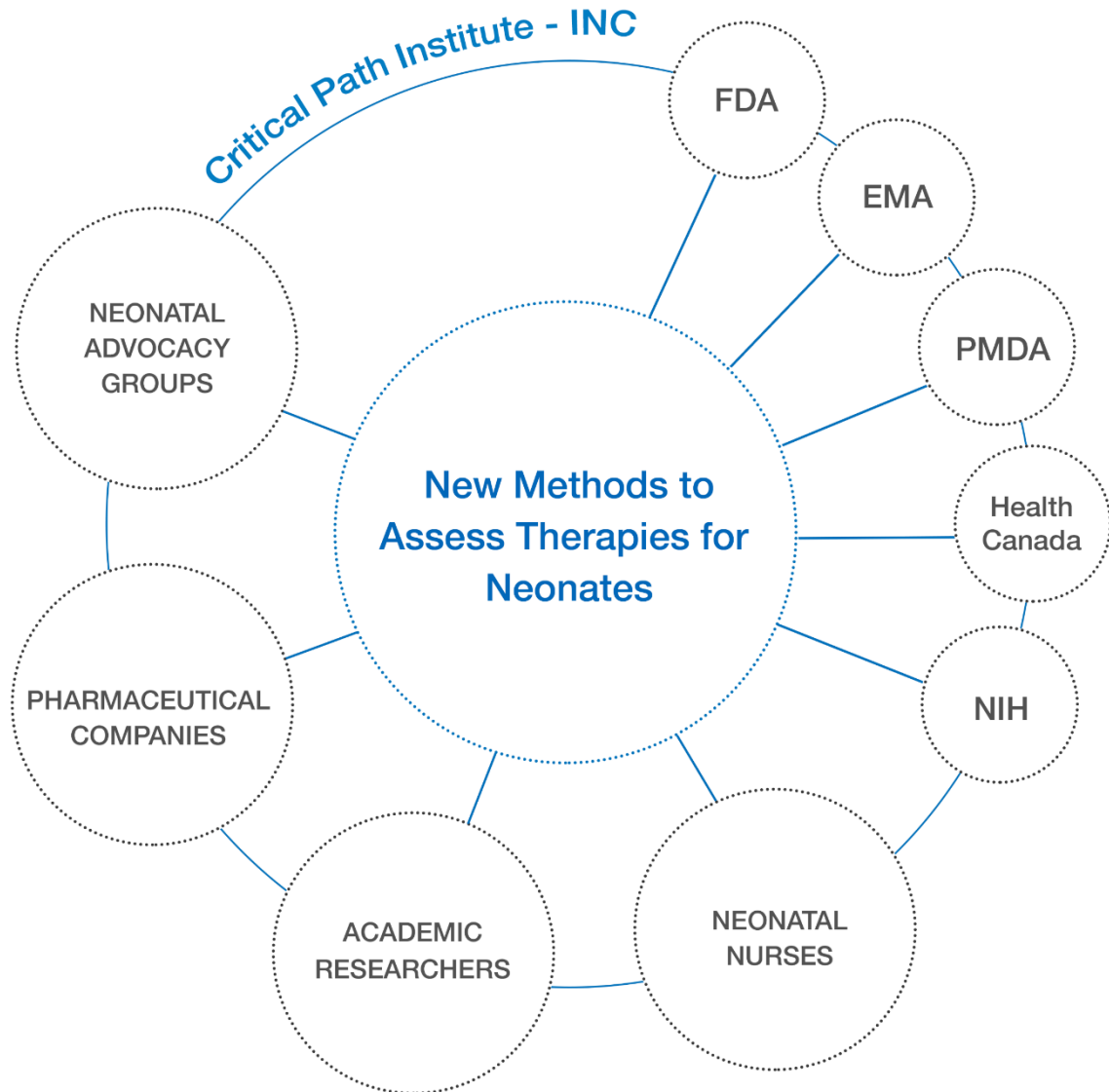


Denver Developmental Screening



- Four Years
 - Dressing without supervision
 - Draws a man with three parts
 - Defines words
 - Hops on one foot
 - Plays interactive games

Members Spanning the Globe



Neonatal Nurses

- NANN
- COINN

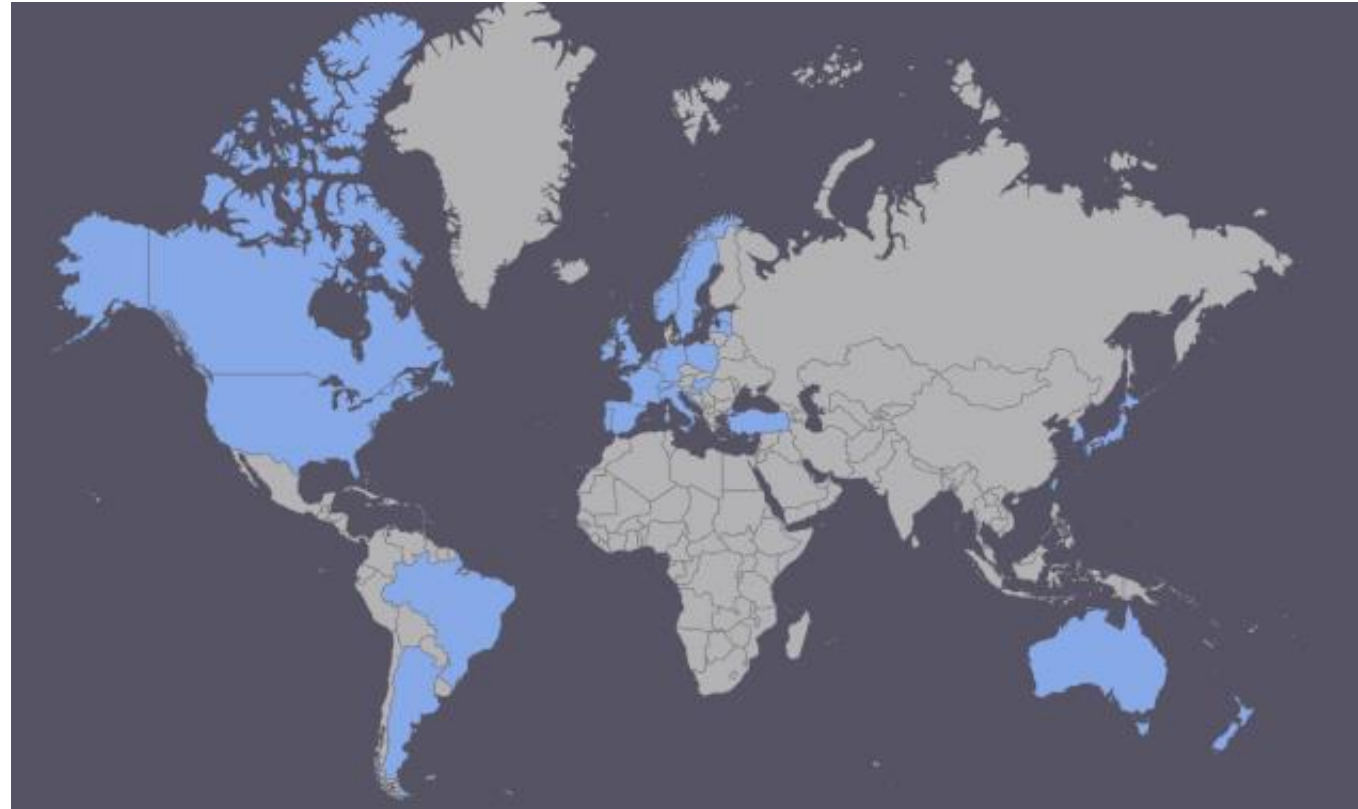
Companies

- Baxter
- Bayer
- Chiesi
- Infant Bacterial Therapeutics
- Johnson & Johnson
- Eli Lilly
- Novartis
- Pfizer
- Sanofi
- Takeda
- Trove Therapeutics

Families/Advocacy

- Bliss
- March of Dimes
- NEC Society
- Premie Parent Alliance
- EFCNI (Consultants)

INC Member Countries – January 2019



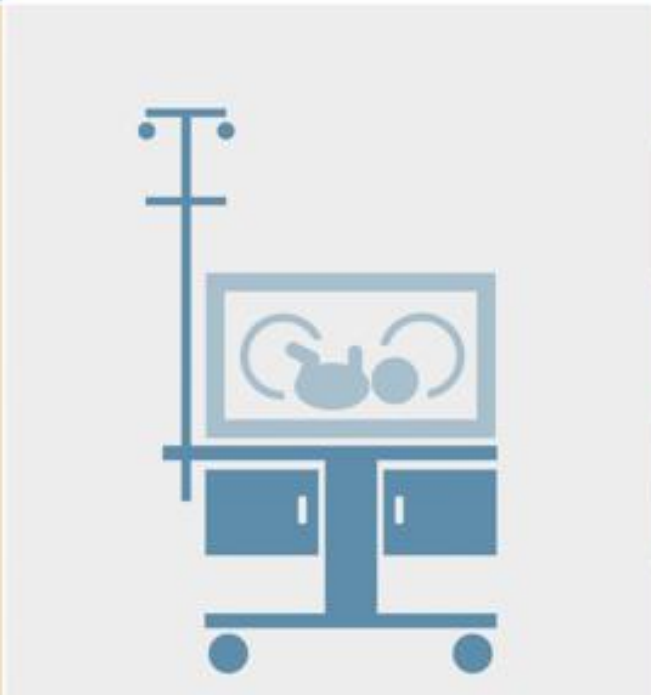
- Argentina
- Australia
- Belgium
- Brazil
- Canada
- Estonia
- France
- Germany
- Hungary
- Ireland
- Italy
- Japan
- Latvia
- Netherlands
- New Zealand
- Norway
- Poland
- Portugal
- S. Korea
- Spain
- Sweden
- Switzerland
- Taiwan
- Turkey
- UK
- USA

INC Priority Conditions



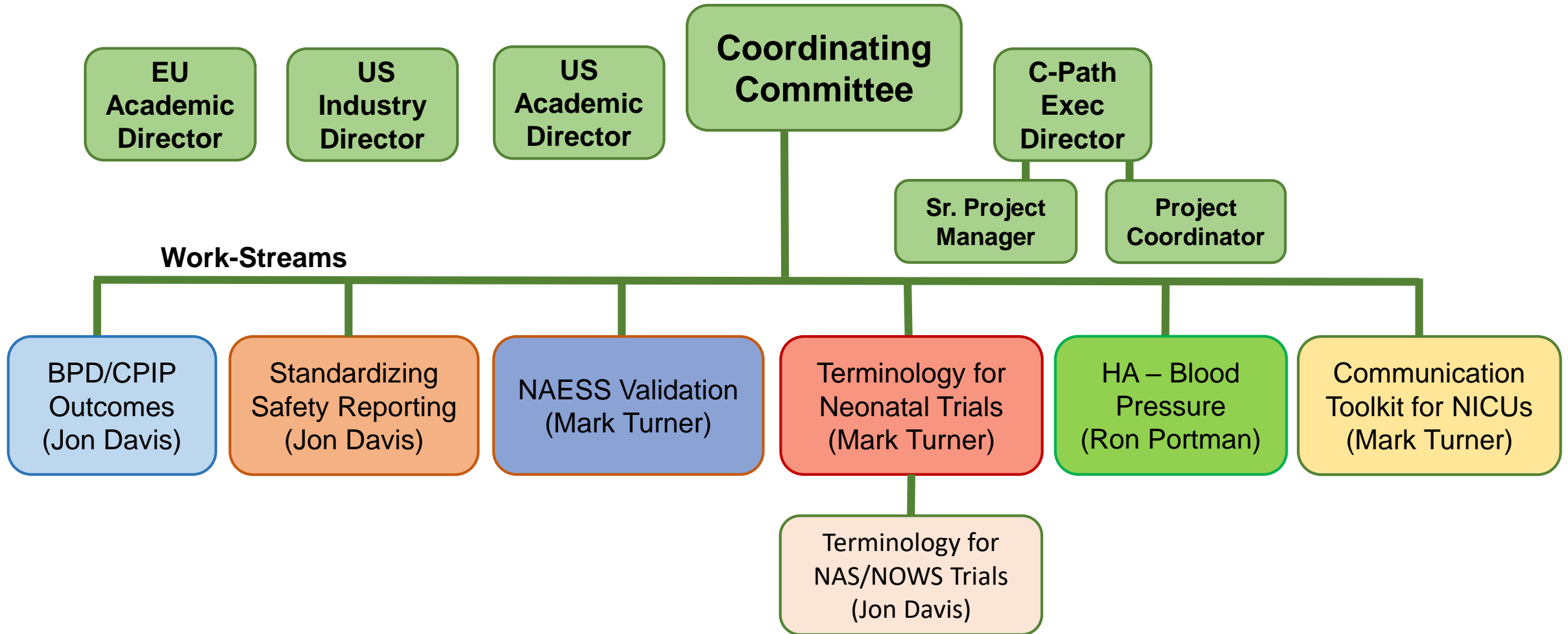
INC AND THE NICU

The International Neonatal Consortium concentrates its efforts on those conditions most commonly encountered in neonatal intensive care units (NICUs), and on the prevention of preterm birth.



- NEONATAL LUNG INJURY AND CIRCULATORY FAILURE
- PERINATAL/NEONATAL INFECTIONS
- NEONATAL ABSTINENCE SYNDROME (NAS)/ NEONATAL OPIOID WITHDRAWAL SYNDROME (NOWS)
- RETINOPATHY OF PREMATUREITY (ROP)
- NEONATAL GASTROINTESTINAL INJURY
- NEONATAL BRAIN INJURY
- DRUGS TO PREVENT PRETERM LABOR
- HEMODYNAMIC ADAPTATION (HA)

INC Governance Structure



Anticipated Future Work-streams: Digital Technologies, Pain

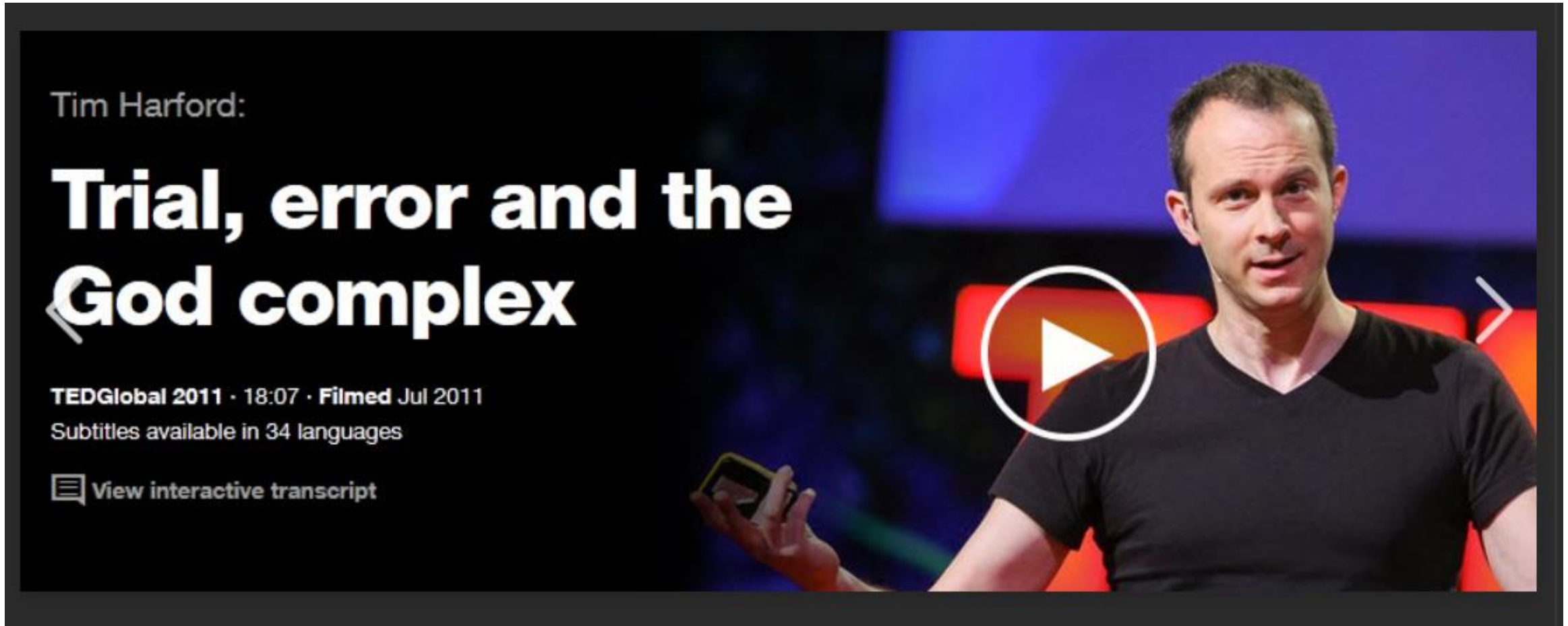
LAUNCH 1ST ANNUAL WORKSHOP

PUBLISHED MANUSCRIPTS

2015	Reg. Sci. to Develop Safe Medicines for Neonates. <i>Ther Innov Regul Sci. 49:623 (2015)</i>	Observed Ranges of Blood Pressure Measurements in Neonates (Planned)	2020
2015	Global Collaboration to Develop Drugs for Neonates. <i>JAMA Pediatr. 169:887 (2015)</i>	Factors that Influence Blood Pressure in neonates and infants (Planned)	2020
2015	Global Efforts to Accelerate Newborn Therapy Development. <i>SOATT Newsletter; 2015</i>	Retrospective Validation of the Neonatal Adverse Event Severity Scale	2020
2016	Collaborating to Advance Reg. Sci. for Neonates. <i>Pediatr Res. 80:462 (2016)</i>	Prospective Validation of the Neonatal Adverse Event Severity Scale (Planned)	2020
2017	Safety Dosing and Pharmaceutical Quality. <i>Pediatric Research 81:692 (2017)</i>	NICU Stakeholder Survey Results and Key Messages (In Development)	2020
2017	Framework for Evidence-Based Drug Therapy. <i>JAMA Pediatrics 171:1 (2017)</i>	Proper Method of Blood Pressure Measurement is Critical in Neonates and Infants: A Systematic Review and Analysis (In Development)	2019
2017	Chronic Pulmonary Insufficiency of Prematurity: Endpoints for Drug Development. <i>J Pediatr.;191:15 (2017)</i>	Standardizing Safety Assessment and Reporting for Trials (Submitted to INC Coordinating Committee)	2019
2017	Enrollment of Neonates in More Than One Clinical Trial. <i>Clin. Therapeutics 39:1959 (2017)</i>	Development of a Neonatal Adverse Event Severity Scale (Submitted, Archives of Disease in Childhood)	2019
2018	Sharing Data to Improve Neonatal Care: Standards and Definitions. <i>J Pediatr. 203:437 (2018)</i>	Long Term Neurodevelopmental Outcome Following Trials of Medicinal Products in Neonates (In Review, Pediatric Research)	2019
2018	Recommendations for the Design of Therapeutic Trials for Neonatal Seizures. <i>Pediatr Res. Dec 24 (2018)</i>	Necrotizing Enterocolitis: Improving Diagnosis, Prevention, and Treatment (In Review, Journal of Pediatrics)	2019
		Therapies to Prevent or Treat Retinopathy of Prematurity (In Press JAMA Ophthalmology)	2019

SUBMITTED, IN-DEVELOPMENT, PLANNED MANUSCRIPTS

TED Talk by Tim Harford



Systematic way of determining what's working and what's not

TED Talk by Tim Harford

- Cardiac trial about recovery in hospital or at home after heart attacks
 - Reversed the data when presented
 - Unexpected results
 - How do you deal with the uncertainty and being challenged
- Difficult to make good mistakes



Long-Term Outcomes or How to Learn from Our Successes and Our Failures

- In order to adapt, you need to have the data
 - How do we access all the data?
 - How do we share data?
 - How do we publish negative data?
 - How do we address our feelings of certainty?





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Education Session – Educating the Neonatology Community on the Drug Development Process

Ron Portman - Chair

May 1, 1:00pm – 5:30pm





International Neonatal Consortium

If we cannot stand for babies, who can we stand for?

(Ward and Bucci-Rechtweg)

Ron Portman, Novartis, INC Co-Director



Accelerating the development of safe and effective therapies for neonates.

The consortium will address the need for measurement and assessment of clinical outcomes in neonates through teams that share data, knowledge, and expertise to advance medical innovation and regulatory science.

May 19, 2015



International Neonatal Consortium

Drug Development Educational Session May 1, 2019

*Why aren't drugs being developed for the neonatal population
by the innovator community?*



Innovative Drug Development Specifically for Neonates

- Some neonatal conditions treatable with medications developed for adults but different indications; others solely for neonates as they occur only in this age
- Examples: Bronchopulmonary dysplasia, meconium aspiration, NEC, hyperbilirubinemia, neonatal asphyxia, ROP, neonatal seizures
- Drug development very challenging prospect in a human that is constantly changing and enters the world with variable degrees of maturation and ability to manage drugs
- The heterogeneity of the neonatal conditions such as BPD further complicates diagnosis and therapeutic endpoints
- Small number of potential patients making ROI challenging
- No global regulatory requirement for neonatal only drug development
- Current incentives not successful in stimulating innovative neonatal drug development
- Lessons learned: pediatric oncology community



Objectives of Workshop

- Provide foundational knowledge on innovative, regulated medicines development
- Provide foundational knowledge on pipeline decision-making, including factors that influence Go/No-Go decisions
- Discussion on addressing neonatal needs within the current environment
- Co-Chairs: Gerri Baer, Christina Bucci-Rechtweg, Ed Connor, Ron Portman

- **Pathway to development of innovative drugs for neonatal conditions**
 - Will address
 - investigational drug development for neonatal conditions
 - indication extension by mechanism of action for investigational drugs that are in development for adult diseases but have a novel indication in the neonate
 - Will not address
 - the re-purposing or re-formulation of older drugs

Session I – Setting the Scene.

Session Chair: *Gerri Baer, FDA*

- **History of neonatal drug development: *Bob Ward, University of Utah***
- **Regulatory realities: *Susan McCune, FDA***
- **A drug developers experience: *Laura Fabbri, Chiesi***
- **Q&A and Panel Discussion**

Session II – Harnessing the Science.

Session Chair: *Christina Bucci-Rechtweg, Novartis*

- **Introduction to regulated drug development: *Norman Barton, Takeda***
- **Understanding drug development today: Trends, Impact on Neonatal Drug Development Opportunities: *Chris Milne, Tufts Center for the Study of Drug Development***
- ***Introduction to Pipeline Development: Thomas Miller, Bayer***
- **Q&A and Panel Discussion**

Session III – Addressing Neonatal Needs within the Current Environment.

Session Chair: Ed Connor, I-ACT for Children

- **Panel Discussion**
 - **James Baumberger, AAP**
 - **Jennifer Degl, Speaking for Moms and Babies, Inc.**
 - **Agnes Klein, Health Canada**
 - **Susan McCune, FDA**
 - **Kelle Moley, March of Dimes**
 - **Aprile Pilon, Trove Therapeutics**
 - **Mary Short, Eli Lilly**
 - **Mark Turner, U-Liverpool**
 - **Anne Zajicek, NID/OD**
- **Q&A**

Summation: Christina Bucci-Rechtweg, Novartis



International Neonatal Consortium

Session I – Setting the Scene

Gerri Baer – FDA (Chair)





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History of Drug Studies in Newborns

Robert M. Ward, MD, FAAP, FCP
Professor Emeritus, University of Utah



What has increased the study of drugs in newborns and what has not

- FDA & C act of 1962 required study of safety and efficacy for approval of a new drug
- 1968-9: Harry Shirkey, MD, Immediate Past Chair of the AAP Committee on Drugs (COD), Editorial: **Therapeutic Orphan. “Since 1962 they [infants and children] have been denied the use of many new drugs.”** J Pediatr 1968 Jan;72:119-20, reprinted in Pediatrics 1969;104:583-4.
- 1974: COD stated, “However, the Committee feels that clinical studies for most new drug entities should include infants and children during phase II and III; then, by the time of New Drug Application (NDA) approval, sufficient data would be available to prevent "orphaning."
- 1975: John Wilson: 78% of drugs listed in the PDR lacked adequate pediatric prescribing information. “Pragmatic assessment of medicines available for young children and pregnant or breast-feeding women.” In: Basic and Therapeutic Aspects of Perinatal Pharmacology. New York, NY: Raven Press; 1975: 411–421
- 1977 AAP Committee on Drugs publishes “Guidelines for the Ethical Study of Drugs in Children” *Pediatrics* 1977;60;91-101
- 1994 Final Rule establishes the concept of extrapolation of efficacy if a disorder and response to treatment are similar in adults and children; continued in FDAMA and BPCA (21 CFR Part 201 [Docket No. 92N-0165])

The Carrot and the Stick

- 1997 FDA Modernization Act (Congressional Law): incentives of market exclusivity extension in return for pediatric studies of new drugs that conform to a Written Request before market exclusivity expired
 - Voluntary program
 - Required a list of drugs considered important to study
 - AAP COD tried to help
- 1998 Final Rule (FDA Regulation): required studies of new drugs if they likely offered therapeutic benefit to children or were known to be widely used to treat children

- **2001 Report to Congress:** Neonates don't have the same incentives for studies
 - “There is currently an inadequate incentive to conduct pediatric studies in certain younger age groups when those studies must be deferred until additional information has been gathered from studies in older children or from other sources.
 - **To encourage studies in these younger age groups, especially neonates, an additional incentive could be provided.** FDA believes this may be advisable because it is clear from its experience that Written Requests issued by the Agency frequently do not request studies in neonates and younger pediatric age groups for scientific, medical or ethical reasons.”
 - Justification for delayed neonatal studies may not be scientifically justified

<https://www.fda.gov/downloads/ScienceResearch/SpecialTopics/PediatricTherapeuticsResearch/UCM517812.pdf> P. 20

History: Experiments That Sort of Worked

- October 17, 2002, Judge Henry H. Kennedy in the District removed the 1998 Final Rule; “it exceeded FDA’s authority”; ‘although it might be the best solution for a difficult problem.’
- 2002 Best Pharmaceuticals for Children Act (**BPCA**) continued incentives; added NIH Foundation to study widely used, off-patent drugs without a pediatric label
 - Funding through voluntary donations from PhRMA failed; NIH institutes-taxed
- 2003 Pediatric Research Equity Act (**PREA**) by Congress re-established almost all of the 1998 Final Rule
- 2007 renewal of PREA and BPCA with additional provisions for devices and biologics
- 2012 PREA and BPCA made permanent, but not all the provisions.
- 2016 Report to Congress by Rob Califf: over 600 pediatric label changes, but “Despite this, studies in neonates, infants, and rare diseases remain a challenge.”
 - <https://www.fda.gov/downloads/ScienceResearch/SpecialTopics/PediatricTherapeuticsResearch/UCM509815.pdf>

Another Effort to Increase Studies in Newborns

NICHD: 2004 Newborn Drug Development Initiative

- ✓ Collaboration between NICHD led by Dr. Giacoia and the FDA led by Dr. Birenbaum
- ✓ Experts in Neurology, Cardiology, Pulmonary, Pharmacology, Pain Control and Ethics described the primary disorders in newborns and recommended study designs
- ✓ Little progress: large number of drugs needed study, BUT limited appropriate formulations, limited sites for study, limited number of patients, limited funds, off-label treatment was acceptable to most neonatologists. (What else could you do when treatment was needed?)
 - ✓ *Clin Ther* 2005;27:796-813. *Pediatrics* 2006;117:S1-8

- FDAMA required a list of drugs prioritized for study, but it was ineffective for a voluntary program.
 - ✓ As chair of COD in 1997, I asked all of the AAP sections and committees for a list of prioritized drugs but few responded, so I made a list and asked for feedback from AAP Sections – another failure; the requirement of a list was dropped in 2002 in BPCA.
- No list identifies new drugs that are a priority for pediatric study, much less neonates

- 2002 BPCA Established the NIH Foundation to study off-patent drugs
 - ✓ Required development of a process to secure funds, identification of drugs to study, selection of sites, monitoring of studies; all new functions for NICHD
 - ✓ A few studies were started
 - ✓ Unanticipated complications: Off-patent drugs considered for study sometimes were on-patent again and did not qualify
 - ✓ Studies needed to comply with the requirements of the FDA; required new collaboration
 - ✓ After completion of adequate study for labeling, who can change the label?; who owns the label??
 - ✓ The original innovator sponsor owns it, but may have sold the drug or been taken over by another company or may not want to spend the money to change the label
 - ✓ **2007 no new labels of off-patent drugs**

NICHD to the rescue: Pediatric Trials Network

Duke Clinical Research Institute, Danny Benjamin, MD, PhD PI led the way with help from several younger investigators: Mickey Cohen-Wolkewicz, Brian Smith, Christof Hornik and others

- ✓ Awarded 9/2010, first patient 1/2011
- ✓ Strict timelines for contracting, IRB approval first patient enrolled, and total enrollment
- ✓ Complemented by collaboration between FDA led by Dianne Murphy (FDA) and NICHD led by Anne Zajicek to find a way to label older drugs (publish proposed label in CFR, seek comments)
- ✓ **2019: 26 clinical trials, 12 other studies, 10 label changes, 21 submissions for label change pending, >7000 children enrolled in 18 therapeutic areas.**

How Much Did PREA and BPCA Benefit/Harm Newborns?

- Review of studies submitted to the FDA through PREA and BPCA (1997-2010) to determine labeling and medication use in neonatal care. Laughon et al. *JAMA Pediatr.* 2014;168(2):130-136.
 - ✓ 406 Pediatric label changes → 24 Neonatal label changes → 13 No neonatal indication → 11 Neonatal indications
 - ✓ 41 studies of 28 drugs included neonates
 - ✓ Analysis of the use of these 28 drugs in 446,335 neonates (Pediatrix data base)
 - ✓ **28 drugs: 13 (46%) NEVER USED; 8 (29%) used <0.013% of neonates**
 - ✓ Of 7 drugs used frequently, ranitidine, used most often, is considered inappropriate for most neonatal therapy
 - ✓ **Of the 28 drugs studied, 75% were useless studies in newborns who never or rarely use the drugs**
 - ✓ **Such studies represent unethical exposure to a drug with little or no prospect of benefit to the patient**

NEWBORNS REMAIN THERAPEUTIC ORPHANS in need of a better approach to study

Typical Response to Studying Drugs in Neonates

- **FDA: General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products Guidance for Industry. A draft guidance. 12/2014**
- Neonates are mentioned 8 times in the 28 page text, almost always to describe how difficult it is to study this population

<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425885.pdf>

- Response to the FDA about areas in neonatal drug trials and therapy that needed to be covered, authored by Ward, Benjamin and others.
 - Supported by over 775 neonatologists and pediatric clinical pharmacologists
 - Became the outline for the first INC White Paper:
 - Considerations Regarding Safety, Dosing, and Pharmaceutical Quality for Studies that Evaluate Medicinal Products (including Biological Products) in Neonates. *Pediatr Res.* 2017 May;81(5):692-711

How Much Did PREA and BPCA Benefit Newborns?

- Institute of Medicine was required to evaluate the effectiveness of BPCA and PREA. *Safe and Effective Medicines for Children. Pediatric Studies Conducted Under the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act. 2012*
 - ✓ With respect to neonates: **“the limited testing of medications in this vulnerable age group is a continuing concern.”** p. 141

- FDAMA passed in 1997 through the hard work of advocacy groups, especially the AAP and the HIV community, who visited Congressional leaders and testified before Congress about the need for new drugs for their children in dosage forms that they could measure accurately and swallow
- When I testified before Congress, I was politely acknowledged and then came the cameras, the press and a standing-room-only audience to hear Paul Glazer, Hollywood star, who talked about his wife acquiring HIV from a transfusion and unknowingly passing it on to their child.
- FDAMA, BPCA and PREA have worked: by 3/31/2019, **778 labels have changed to include pediatric prescribing information**. PREA is the leading source of new studies, rather than BPCA.
 - <https://www.accessdata.fda.gov/scripts/sda/sdNavigation.cfm?filter=&sortColumn=14a&sd=labelingdatabase&page=1>

- Newborns are still not being studied in a way that improves their drug treatment
- If we are going to learn from our past, the academic, neonatal community needs to organize through collaboration with families and mobilize support through Congress to modify our current approach

To keep history from repeating itself

- History: we continue to need research of drug treatment of all children
- New Recognition: Newborns are still Therapeutic Orphans, left out of meaningful studies of drugs needed to guide treatment in the NICU throughout the country in thousands of newborns, particularly those at the extremes of survival, ELGANS (extremely low gestational age newborns)
 - Drugs need to be identified that are used daily in the NICU, especially those with a narrow therapeutic index, those for critically ill newborns, and those used frequently without dosing based on clinical trials.
 - Studies will only be succeed through a new approach that requires and rewards study of the most important drugs for newborns
 - **That new approach will only succeed with support from parents, researchers, sponsors, and non-profit organizations such as INC and IACT**



International Neonatal Consortium

Considerations On the Drug Development Process for Trials in Neonatology

*Susan McCune, M.D.
Director, Office of Pediatric Therapeutics
Office of the Commissioner, FDA*

*International Neonatal Consortium
Educating the Neonatology Community
on the Drug Development Process
May 1, 2019*



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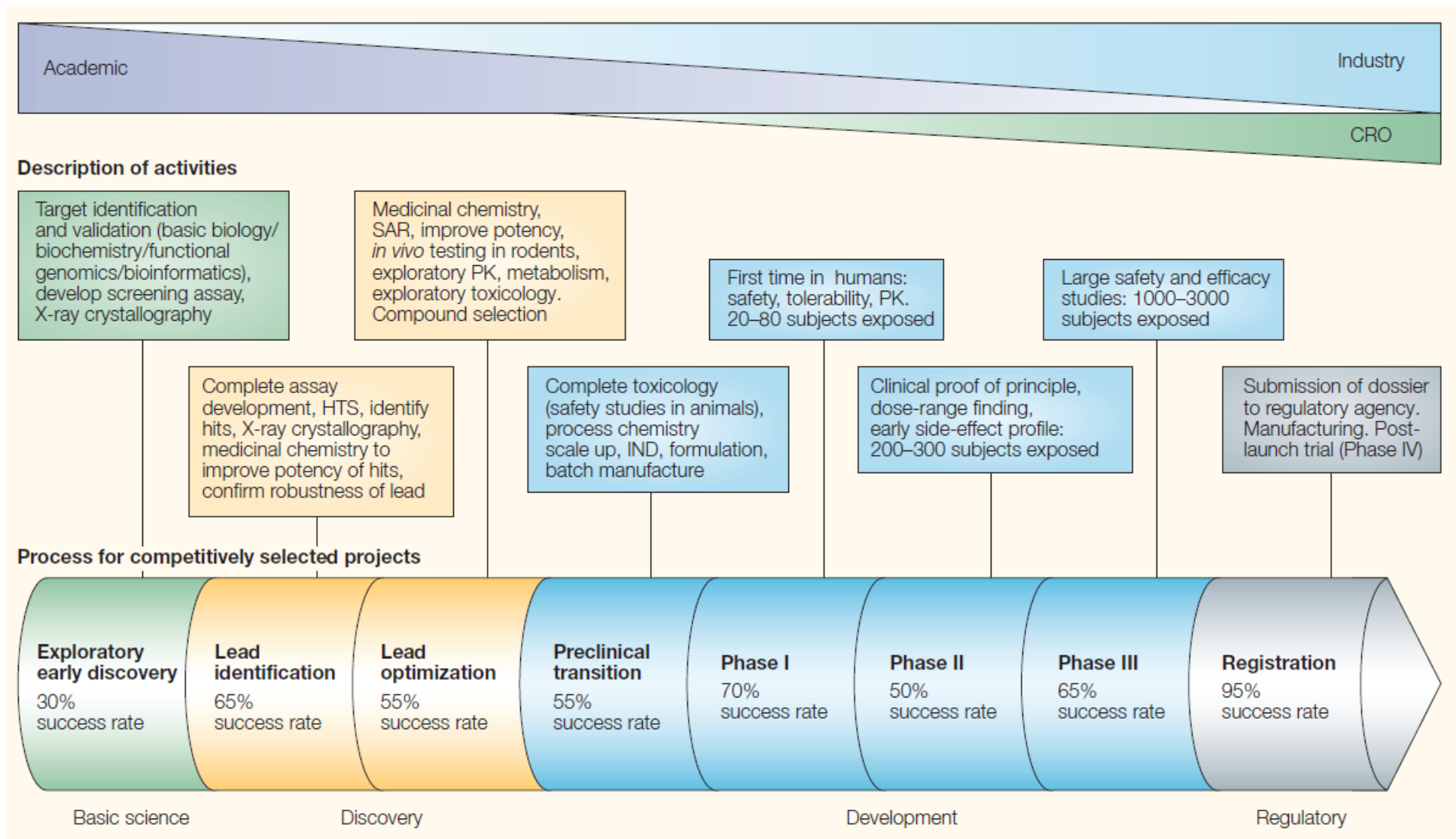


Realities of the 21st Century



- Two decades ago we lacked effective treatments for most life-threatening illnesses
- Today many more treatments are available, but patterns of drug manufacturing, use and guiding information have shifted dramatically
- Patients and clinicians want more accurate, up-to-date and understandable information to ensure safe use and they want it earlier
- New science promises accelerating product development but delivery has lagged
- FDA is only one part of an extremely complex healthcare system. Influencing change is challenging and requires collaboration

Drug Development Overview



Need For Collaboration

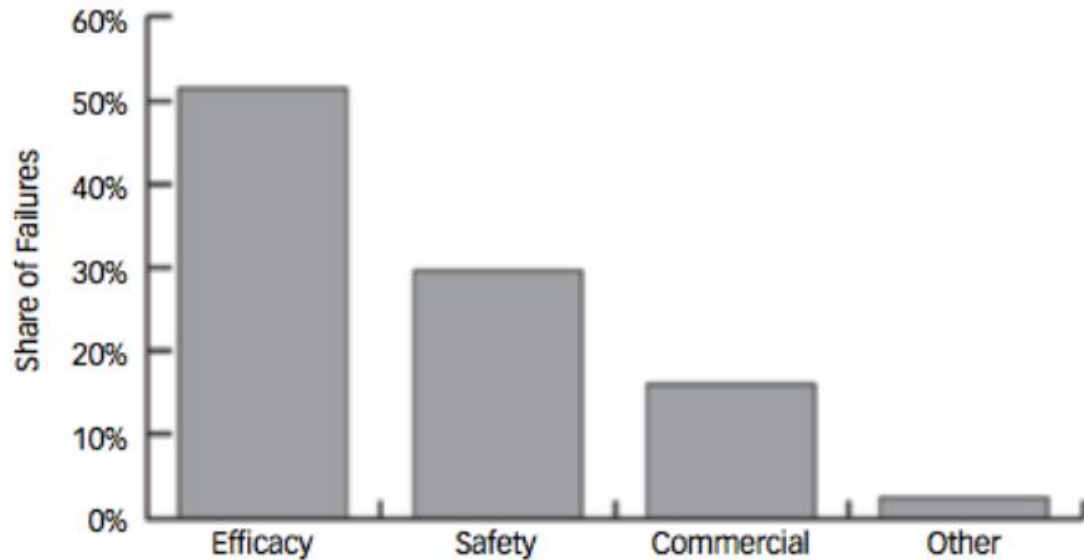


Table 3 | **Organizations involved in R&D for neglected diseases**

Partnering organizations	Strengths	Weaknesses
Big pharma	Strong drug R&D expertise; strong regulatory affairs; strong project management; strong marketing; internal resources for projects	Bureaucracy: slow decisions; a culture of controlling R&D collaboration
Small pharma/ biotech	Specific drug R&D expertise; flexibility of decision making	Drug R&D expertise not complete; market knowledge often limited; often lack internal resources for projects
Academia	Strong basic research: biology/ genomics, target identification/ validation; understand disease and can think 'out of box'	Drug R&D expertise limited; desire to publish early can conflict with patenting; not used to project management; limited commercial understanding
CROs/ consultants	Strengths in specific areas of expertise: management support, regulatory, dossier preparation, toxicology	Few have broad expertise; where expertise is broad, might bring bureaucracy; usually have to pay going market rates
Big public (WHO/TDR)	Knowledge of multiple diseases, health needs and systems in context; links to governments; strong networks in disease-endemic countries; capacity-building focus	Bureaucracy: slow decisions
Small 'public' (MMV, GATB)	Focus on specific diseases; flexibility of decision making	Young organizations: no products delivered yet; limited developing-country experience

Why Drugs Fail

Reasons for Failures



Source: Tufts Center for the Study of Drug Development (CSDD)

Figure 1. The reasons attributed to Phase III clinical trial failures by percentage.

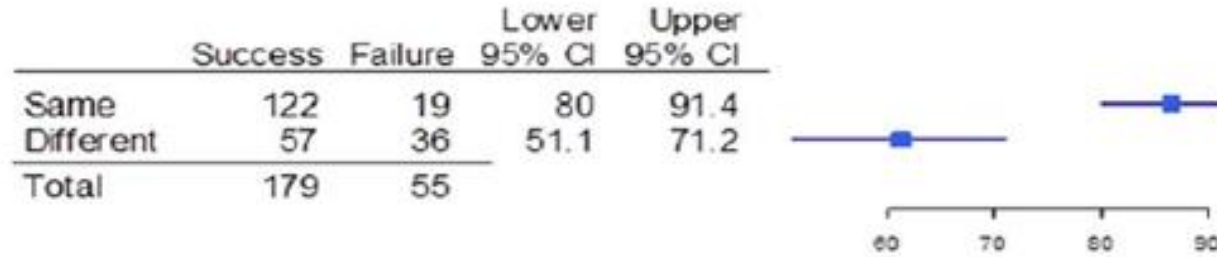
- Approximately 70% of Phase 2 trials are unsuccessful
- Approximately 50% of phase 3 trials fail

Lessons Learned from Failed Pediatric Trials



- Approximately 25 - 40% of pediatric trials fail to establish safety and/or efficacy and result in a labeled indication for pediatric use
 - BUT, the situation is improving through an understanding of pediatric study design issues
- Contributing factors to trial failure
 - Suboptimal dosing
 - Differences between adult and pediatric disease
 - Inadequate trial designs
- Trial design challenges
 - Feasible designs for small patient populations
 - Placebo effect (limits ability to detect effective therapies)
 - Appropriate endpoints (particularly adult vs. pediatrics)

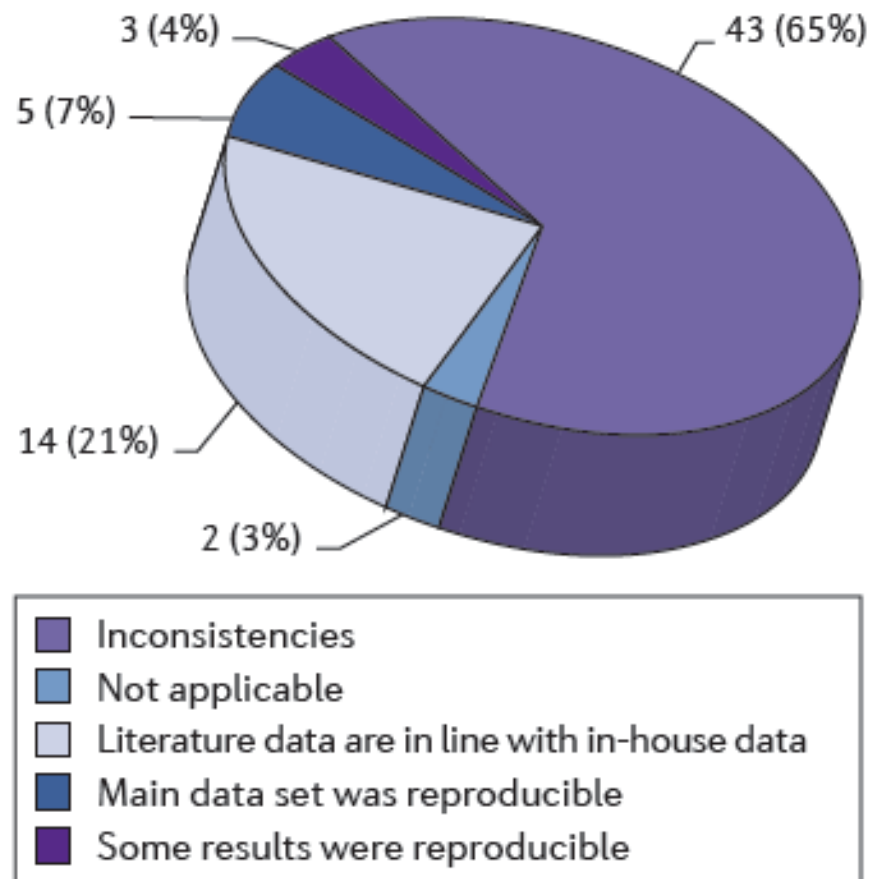
Pediatric Trial Outcome by Whether the Pediatric & Adult Endpoint Were the Same



Examples – Failed Trials Where the Adult & Pediatric Endpoints Were Not the Same

Indication	Ped Age Grp	Ped Endpoint	Time of Measurement	Adult Endpoint	Time of Measurement
Pulmonary Arterial Hypertension	1 - 17 yrs	Percent change in VO2 peak	16 wks	6-minute walk	12 wks
Chronic HBV	2 – 17 yrs	HBV DNA <1000 copies/mL & ALT normalization	48 wks	Histological improvement (biopsy)	48 wks
Bronchospasm	0 - 5 yrs	Daily asthma SS; Ped Asthma Caregiver Assessment	4 wks	FEV1	12 wks

Reproducibility of Published Data



Relationship of published data to in-house data (Bayer HealthCare) for drug targets

Characteristics of the New Paradigm

- Partnership opportunities
- Adjunctive methodologies to improve predictability
- Innovative trial designs
- Optimal use of data
 - Standardization
 - Qualification of drug development tools
- Improved communication
- Innovation in regulatory review

- What is the quality and robustness of the evidence of an effect (including the totality of the evidence)?
- Given that it exists, how meaningful will this effect be in the overall context of the disease? How much will it matter to patients?
- If it matters, what would be the impact of failing to provide this benefit, if real?
- This reasoning has to be weighed against the potential harms of the intervention



- Carglumic acid for N-acetylglutamate synthase (NAGS) deficiency
 - Rare urea cycle disorder (~ 10 patients in U.S.)
 - Retrospective review of a 23 patient case series in Europe
 - Short-term (ammonia) and long-term (neurocognitive) outcomes
 - Compared to historical control (not formally conducted)
- Deferiprone for transfusional iron overload in patients with thalassemia syndromes not responding to other therapies
 - Planned pooled analysis of patients from several studies (n=236)
 - Endpoint was change in serum ferritin, not a clinical outcome
- Cysteamine bitartrate for nephropathic cystinosis
 - 2 open-label studies (n=94) children treated with product or innovator cysteamine HCl
 - Largely a pharmacodynamic comparison based on WBC cystine levels vs. historical control pharmacokinetic/pharmacodynamic levels



- Alglucosidase alfa for Pompe Disease: survival data from an international registry of infantile-onset disease
- Cholic acid for bile acid synthesis disorders: data on growth, survival and reduction in abnormal cholestatic markers in a case series
- Glucarpidase for MTX toxicity: data on approx. 20 patients from NIH treatment protocol

Nusinersen for Spinal Muscle Atrophy



- Approved by FDA in December 2016 and marketing authorization granted by European Commission in June 2017
- Fast track designation and priority review
- Orphan drug designation
- Received a rare pediatric disease priority review voucher

Nusinersen for Spinal Muscular Atrophy

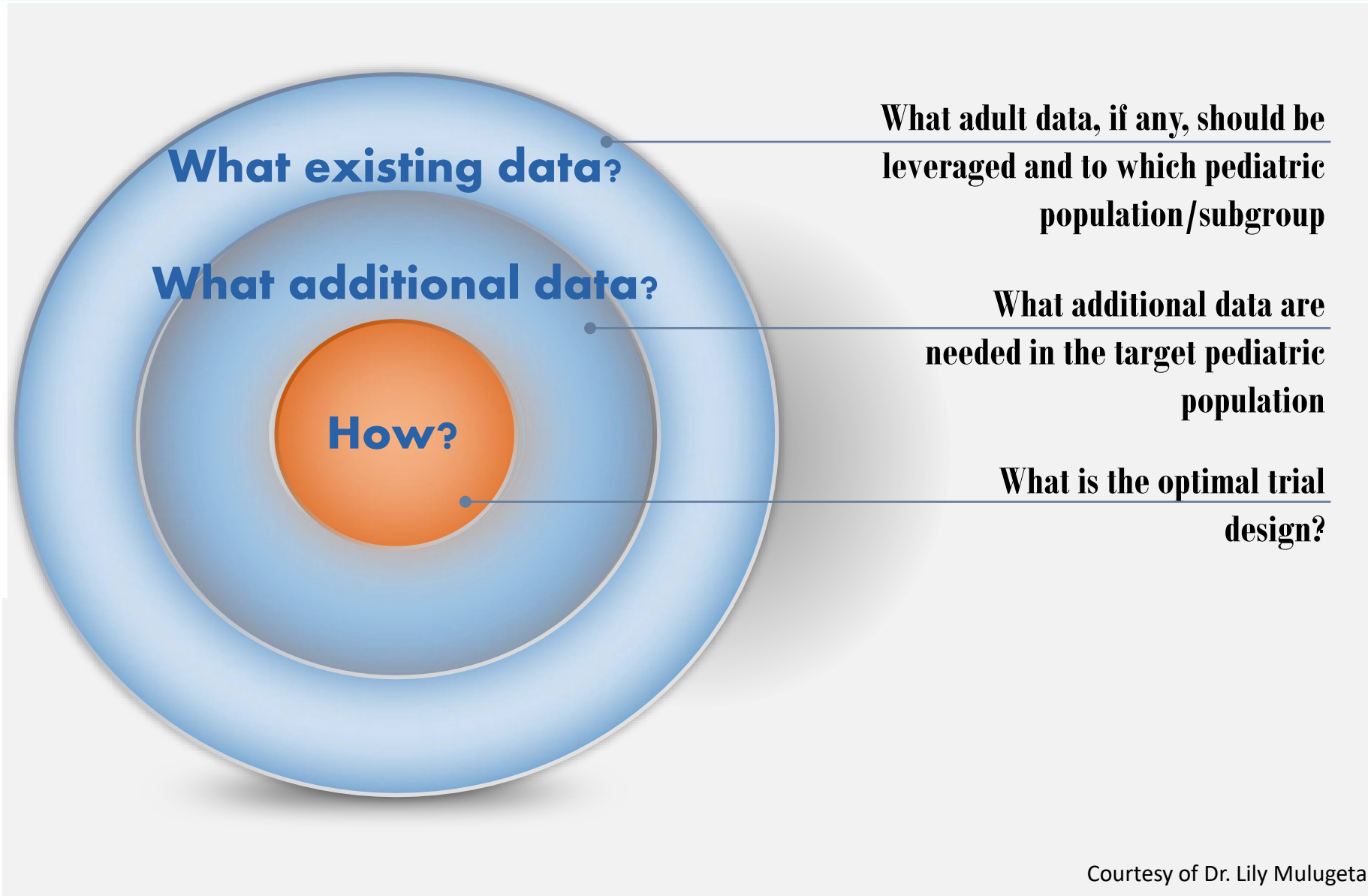
- **Population**
 - SMA SMN2 copy number (2 copies in 98% of subjects in both groups)
- **Trial Design**
 - Multicenter, randomized, double-blind, sham-procedure controlled study in 121 symptomatic infants ≤ 7 months of age
 - Patients randomized 2:1 to receive nusinersen or sham
 - Interim efficacy analysis based on patients who died, withdrew, or completed at least 183 days of treatment
- **Endpoints**
 - Primary endpoint at interim analysis was proportion of responders – improvement in motor milestones according to Section 2 of the Hammersmith Infant Neurologic Exam (HINE)
 - Supported by open-label uncontrolled trials in symptomatic SMA patients, age 30 days to 15 years at the time of first dose, and in pre-symptomatic patients, age 8 days to 42 days at the time of first dose

What Did These Have in Common?

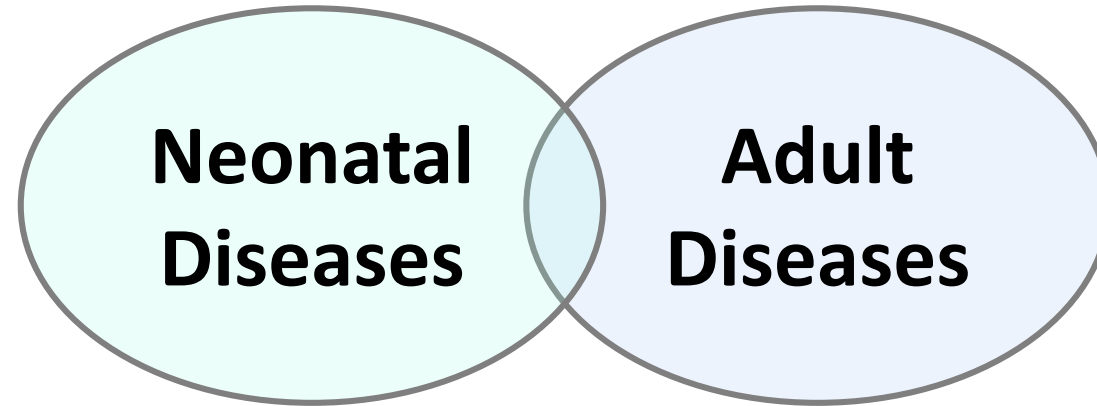
- Highly plausible mechanistic hypothesis
- Natural history data on untreated patients
- Highly plausible biomarkers; most could be measured in a standard manner
- Serious unmet medical need
- Relatively large treatment effect

FDA is Evaluating Use of RWE

- We have approved drugs for rare diseases based on data from registry-like case series
- We have used registry data as external controls
- We are exploring how randomization would work in registry or healthcare settings
- We are collaborating with groups working to improve the validity of key data elements collected in the process of health care
- We have spoken to many groups that are assembling oncology care data in various ways and hope to provide valid platforms for investigations



Drug Development Disconnect

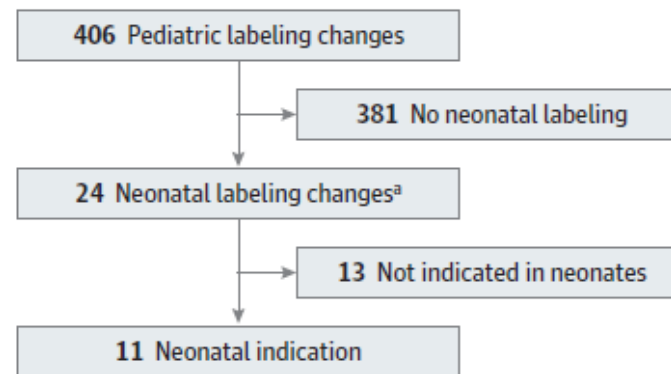


Majority of drugs used are off-label

Very few new therapies are being developed specifically for neonates

Pediatric Plans to include neonates

Figure. Neonatal Labeling Changes Under Legislation From 1997 to 2010 and Exposure of Neonates to Drugs With a Neonatal Indication



28 drugs studied in neonates

- 46% not used in NICUs
- 29% used in fewer than 60 neonates

Laughon MM, Avant D, Tripathi N et al. 2014. Drug labeling and exposure in neonates. *JAMA Pediatr.*168:130-136.

^aThere are 24 neonatal labeling changes involving 23 drugs. Linezolid has 2 labeling changes.

Drug Development Paradigm



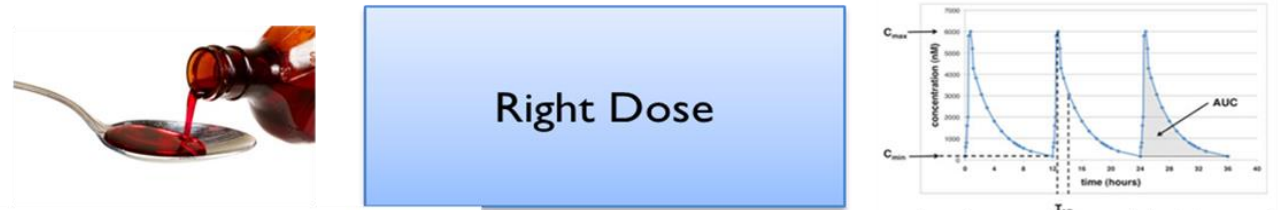
Right Drug



Right Population



Right Dose



<http://www.upci.upmc.edu/ctp/pharmacokinetics.cfm>

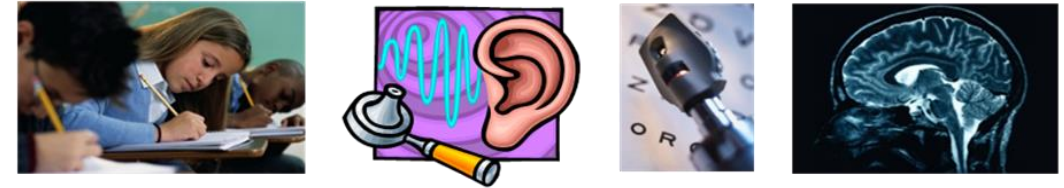
Right Trial Design



<http://www.wfsbp.org/activities/feature-forum-current-issue/archive-single/should-we-accept-enrichment-designs-in-psychiatry/ac3a3fb97cf270c48b2ecd25c825ee9b.html>

<http://accp1.org/pharmacometrics/theory.htm>

Right Endpoints



U.S. Evidentiary Standard for Approval



- For approval, pediatric product development is held to same evidentiary standard as adult product development:
- A product approved for children must:
 - Demonstrate **substantial evidence of effectiveness/clinical benefit** (21CFR 314.50)
 - Clinical benefit:
 - The impact of treatment on how patient feels, functions or survives
 - Improvement or delay in progression of clinically meaningful aspects of the disease
- Evidence of effectiveness [PHS Act, 505(d)]
 - Evidence consisting of adequate and well –controlled investigations on the basis of which it could fairly and responsibly be concluded that the drug will have the effect it purports to have under the conditions of use prescribed, recommended, or suggested in the labeling



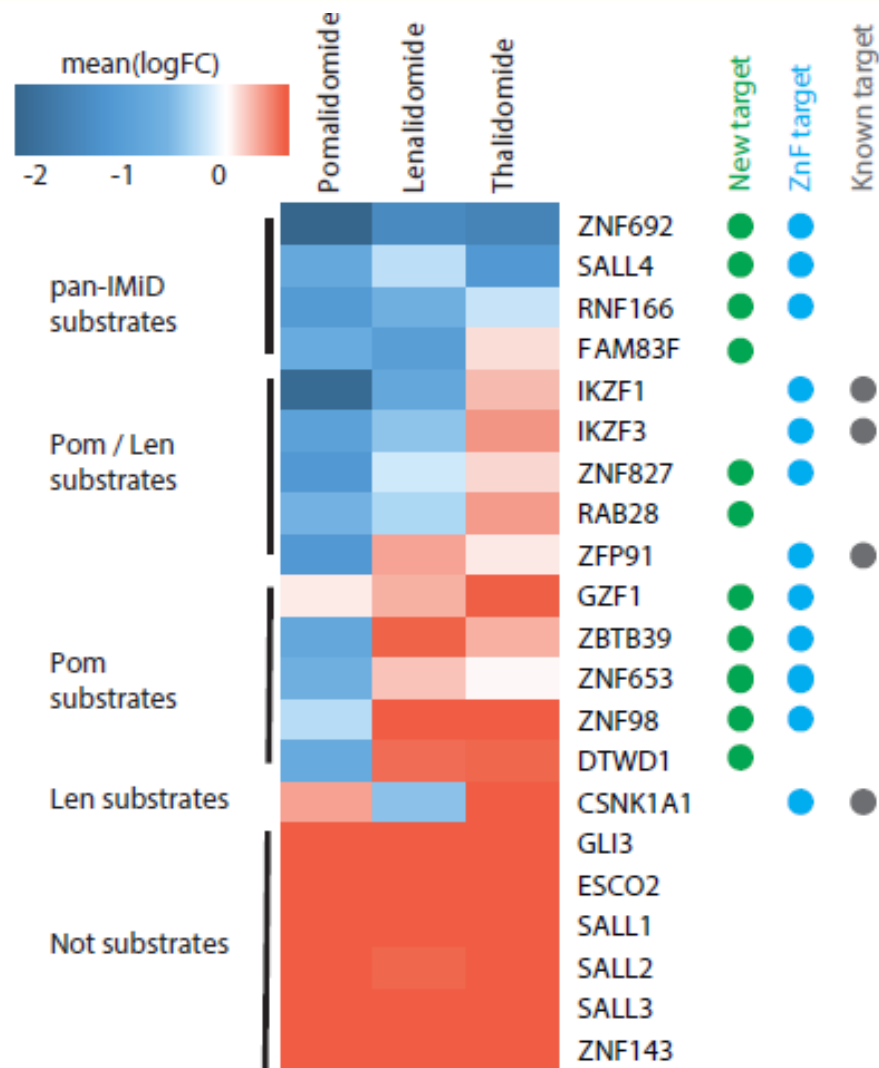
- Disease pathophysiology
 - Natural history
- Drug mechanism of action
 - Ontogeny of organ/receptor systems
- Potential use of non-clinical models
 - Understand potential safety and efficacy
 - Animal models
 - In silico models
- Best intentions
 - Oxygen for preterm infants in 1950's (ROP)
 - Chloramphenicol (gray baby syndrome)
 - Steroids for preterm lung disease (neurodevelopmental disability)
 - 100% oxygen resuscitation in the DR (adverse outcomes)

Thalidomide



- 1960 Merrell Company of Cincinnati submitted a new drug application for Kevadon, the brand name of a sedative that had been marketed in Europe since 1956: Thalidomide
- Medical officer felt that the data were incomplete to support the safety
- 1961 the drug was pulled off the market in Germany because of congenital anomalies
- Over 20,000 Americans received thalidomide under the guise of investigational use
- 1962 Kefauver-Harris Amendment that manufacturers had to prove efficacy as well as safety

Thalidomide



- Thalidomide and IMiD drugs disrupt a broad transcriptional network through induced degradation of several C_2H_2 zinc finger transcription factors, including *SALL4*, a member of the *spalt*-like family of developmental transcription factors
- Heterozygous loss of function mutations in *SALL4* result in human developmental conditions that phenocopies thalidomide induced birth defects such as absence of thumbs, phocomelia, defects in ear and eye development, and congenital heart disease
- Thalidomide induces degradation of *SALL4* exclusively in humans, primates and rabbits but not in rodents or fish

- Understand the neonatal population
 - Disease epidemiology
 - Subgroups of patients
 - Homogeneity/heterogeneity
 - Biomarker enrichment
 - Size of study groups
 - Particular safety issues
 - Proof of concept studies may help define population for larger study

Extracorporeal Membrane Oxygenation (ECMO) in Neonatal Respiratory Failure

100 Cases



FDA

ROBERT H. BARTLETT, M.D. JOHN TOOMASIAN, C.C.P. DIETRICH ROLOFF, M.D.
ALAN B. GAZZANIGA, M.D. ARNOLD G. CORWIN, M.D. RALPH RUCKER, M.D.

- Published in 1986 in the Annals of Surgery
- Major complication was intracranial bleeding which occurred in 89% of patients born at <35 weeks gestation and 15% of full-term infants
- Best survival in persistent fetal circulation (100% survival of 10 patients)



- ADME considerations based on gestational age and postnatal age

Pediatric patients less than 3 months of age

Recommended MERREM IV Dosage Schedule for Pediatric Patients Less than 3 Months of Age with Complicated Intra-Abdominal Infections and Normal Renal Function (2.3)

Age Group	Dose (mg/kg)	Dose Interval
Infants less than 32 weeks GA and PNA less than 2 weeks	20	Every 12 hours
Infants less than 32 weeks GA and PNA 2 weeks and older	20	Every 8 hours
Infants 32 weeks and older GA and PNA less than 2 weeks	20	Every 8 hours
Infants 32 weeks and older GA and PNA 2 weeks and older	30	Every 8 hours

- Intravenous infusion is to be given over 30 minutes.
- There is no experience in pediatric patients with renal impairment.
GA: gestational age and PNA: postnatal age

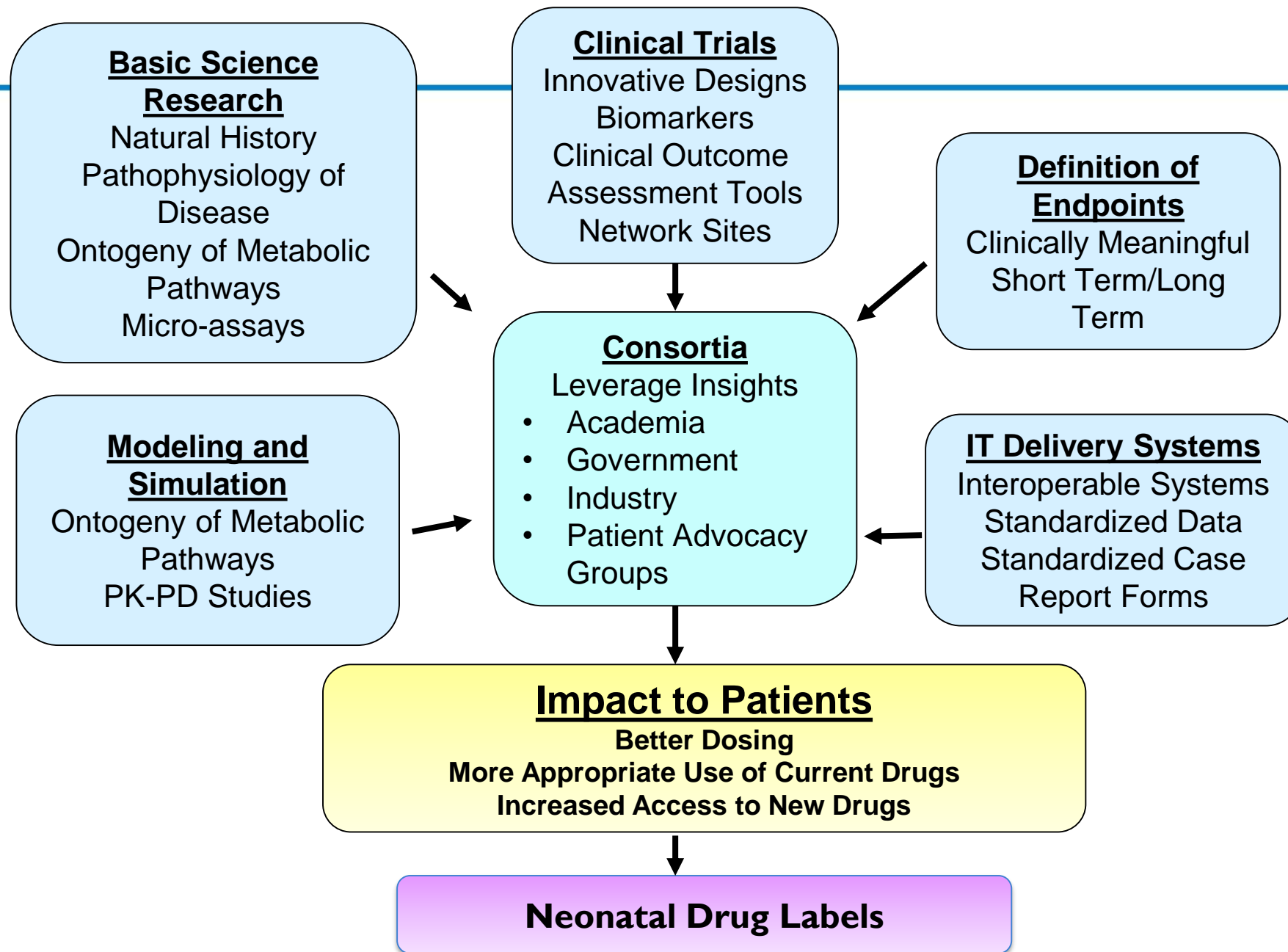
- Innovative approaches as have been used with rare diseases
 - External controlled studies
 - Historical control
 - Registry data
- Leverage all potential data sources to identify gaps
- Potential for use of master protocols

- Clinically meaningful endpoints
- Surrogate endpoints
- Safety endpoints
 - Short-term
 - Long-term

- Clinical outcome assessments (COAs) measure a patient's symptoms, overall mental state, or the effects of a disease or condition on how the patient functions. COAs can be used to determine whether or not a drug has been demonstrated to provide treatment benefit. Treatment benefit can also be defined in terms of a safety benefit compared to other treatments. A conclusion of treatment benefit is described in labeling in terms of the concept of interest, the *thing* measured by the COA
- Four types of COAs
 - Patient reported outcome (PRO) measures
 - Clinician reported outcome (ClinRO) measures
 - Observer reported outcome (ObsRO) measures
 - Performance outcome (PerfO) measures

- FDA Patient Focused Drug Development Initiative meeting 6/10/14
- Wide spectrum of neurological signs and symptoms including seizures, cognitive or behavioral problems, language delay, sleep problems, weakness, difficulty swallowing, balance problems, bowel or bladder problems, pain and other symptoms
- “While each day we deal with the obvious hurdles [like the inability to speak], it’s really the secondary sensory, behavioral, and cognitive symptoms that seem to most impact [my son’s] daily stresses and struggles.”







International Neonatal Consortium

A Drug Developer's Experience

(Chiesi Farmaceutici)

Laura Fabbri

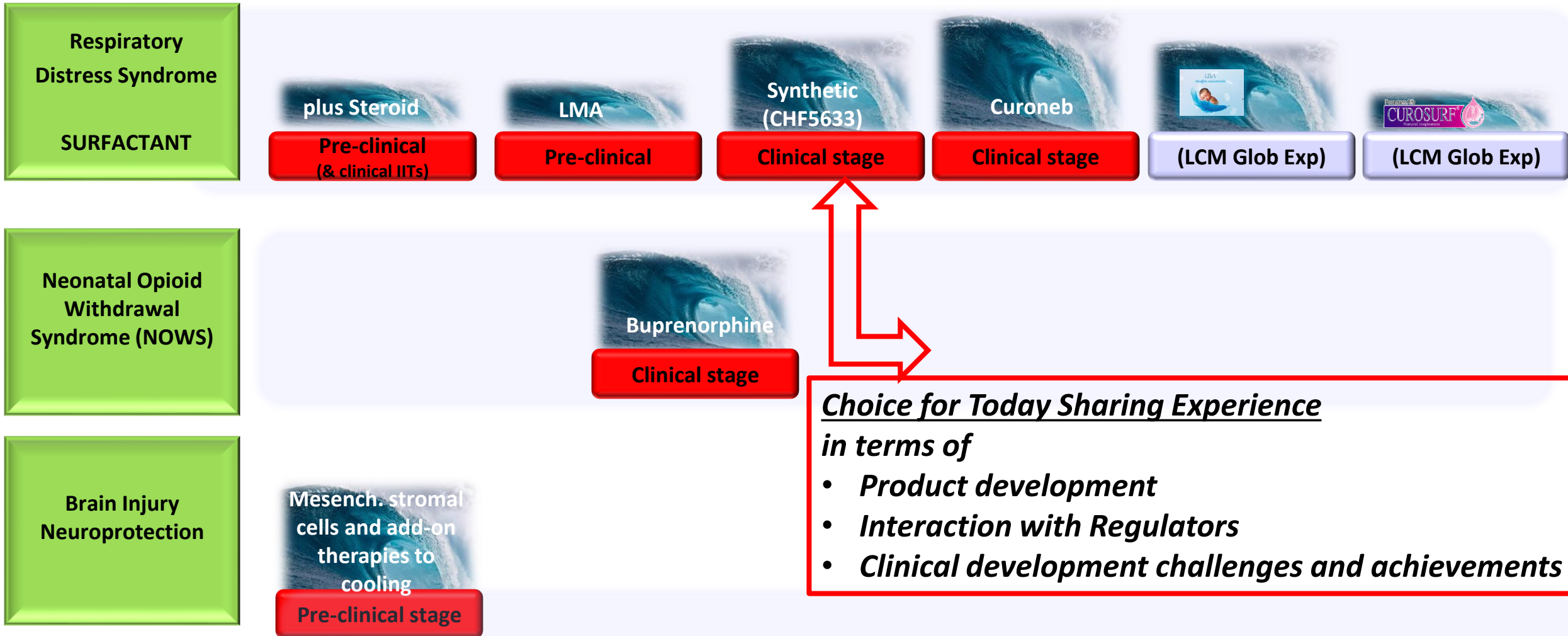
Head of Clinical Neonatology
Global Clinical Development
R&D



Drug Development Pathway & Involved Functional Areas



Neonatology Pipeline/Portfolio



The Research Phase



The Research Phase is devoted to the development of a Lead Candidate (active substance with a demonstrated mechanism of action)

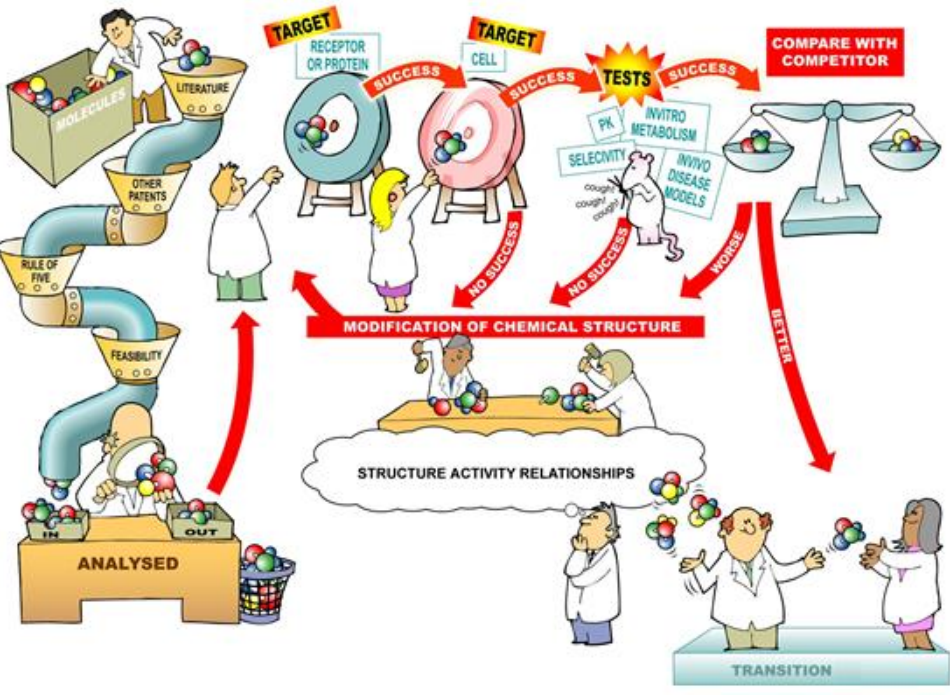
From a driving idea - TARGET PROJECT PROFILE:

- To design a synthetic surfactant very similar to the natural human surfactant and to mimic poractant alfa (Curosurf®)
- with improved resistance to inactivation compared to animal derived surfactants
- representing a back up to Curosurf® to maintain and protect Chiesi leadership in the field of surfactant replacement therapy
- allowing to mitigate the risk of shift toward the use of other synthetic entering the market, to overcome regulatory or religious constrains hampering Curosurf® in some countries

Successful collaboration with **ACADEMIA - Karolinska Institutet and Karolinska University Hospital.**



2000
↓
2006

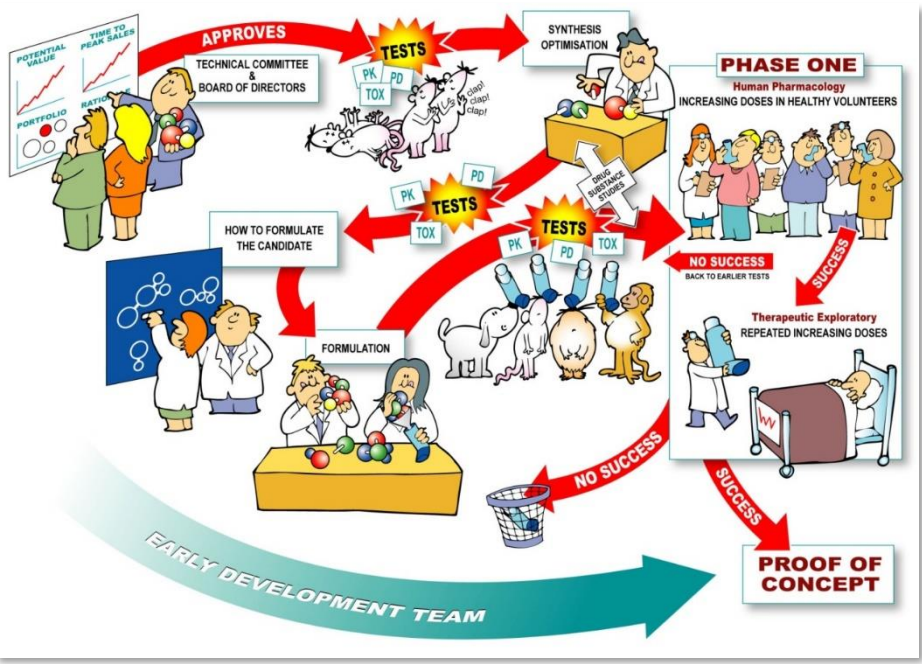


CANDIDATE DRUG

The Learn Phase



The Learn Phase is devoted to establish the so-called “proof of concept” (POC = Evidence of Clinical Safety and Efficacy)



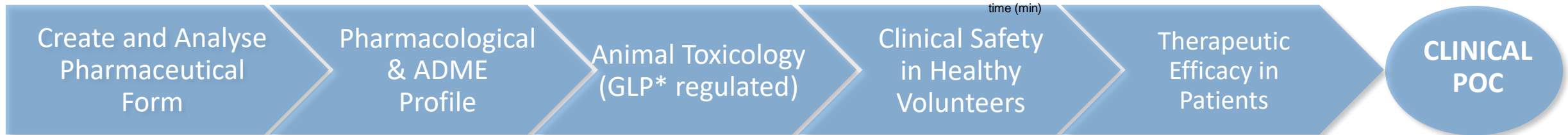
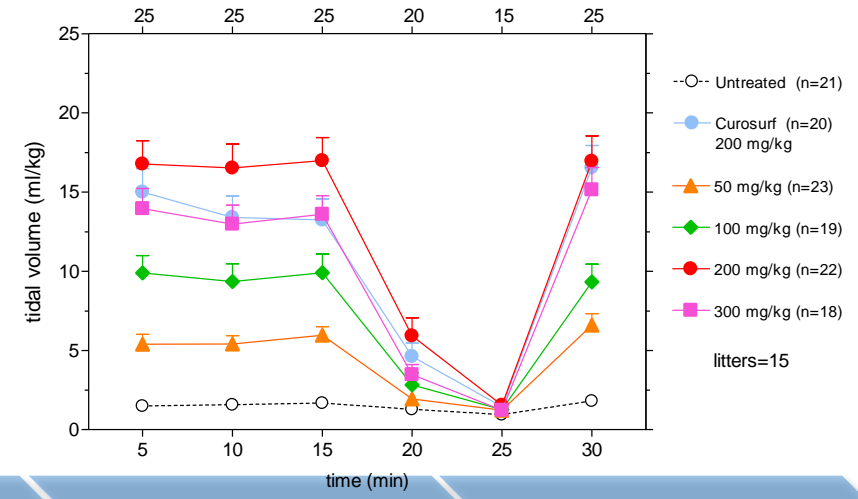
2006
Pre-clinic
2018

Translational Investigation | Articles

In vitro and in vivo comparison between poractant alfa and the new generation synthetic surfactant CHF5633

Francesca Ricci¹, Xabier Murgia², Roberta Razzetti¹, Nicola Pelizzi¹ and Fabrizio Salomone¹

Volume 81 | Number 2 | February 2017 | Pediatric RESEARCH 369



*GLP: Good Laboratory Practices

The Learn Phase



Downloaded from <http://fn.bmj.com/> on May 11, 2017 - Published by group.bmj.com
 ADC-FNN Online First, published on May 6, 2017 as 10.1136/archdischild-2017-312722
 Original article



A first-in-human clinical study of a new SP-B and SP-C enriched synthetic surfactant (CHF5633) in preterm babies with respiratory distress syndrome

David G Sweet,¹ Mark A Turner,² Zbyněk Straňák,³ Richard Plavka,⁴ Paul Clarke,⁵ Ben J Stenson,⁶ Dominique Singer,⁷ Rangmar Goelz,⁸ Laura Fabbri,⁹ Guido Varoli,⁹ Annalisa Piccinno,⁹ Debora Santoro,⁹ Christian P Speer¹⁰

2006

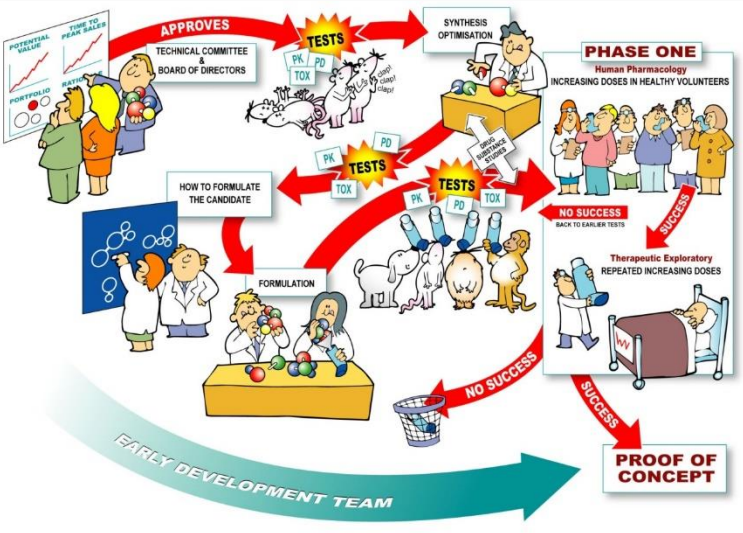
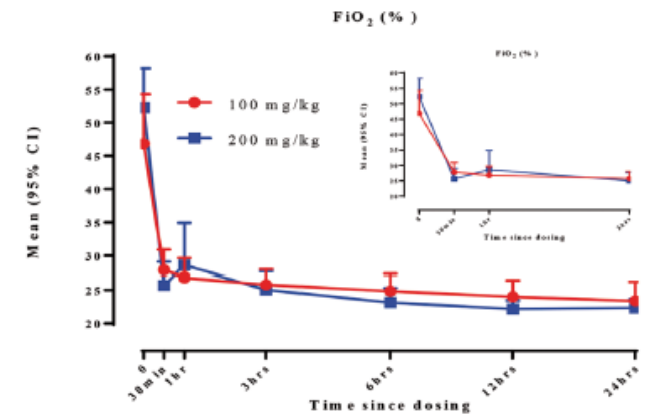
Pre-clinic

- Interaction with National Authorities
- FIH study

2018

What this study adds?

- ▶ This first-in-human trial of synthetic surfactant CHF5633, containing peptide analogues of two surfactant proteins, shows that it was well tolerated without unexpected adverse effects.
- ▶ CHF5633 is similar in volume and appearance to poractant-alfa and appears to work as effectively.



*GLP: Good Laboratory Practices

Main Program peculiarity: straight in preterm neonates (N=40, 27-33⁺6wks GA)

The Learn Phase



Interactions with Agencies in 2010

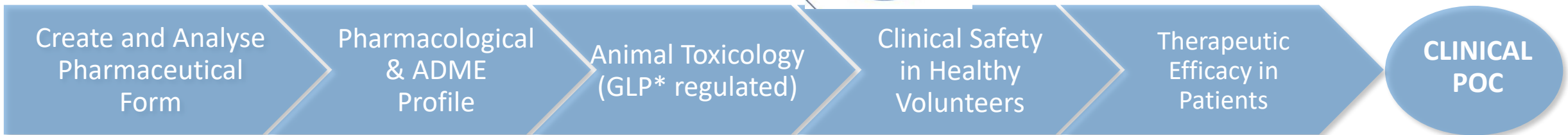
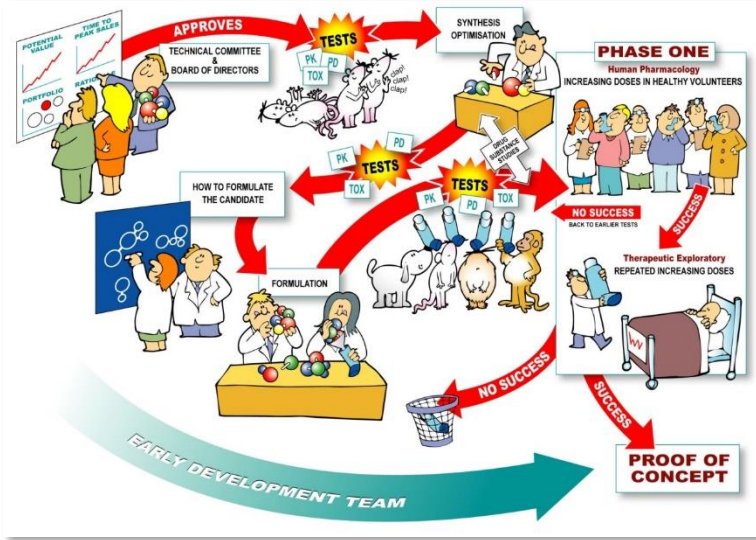
- ✓ Orphan Drug Designation obtained in US and EU
- ✓ Scientific Advice to BfArM (Germany) and MHRA (UK):
 - Does the Agency agree that the proposed quality package is adequate for the First-in-Human clinical trial?
 - Does the Agency consider that the non-clinical package provides adequate information to support First-in-Human clinical trial in preterm neonates?
 - Does the Agency agree that a study in healthy volunteers is not warranted as RDS is a condition that is specific to preterm neonates and that the first study should be in this target population?
 - Does the Agency agree with the proposed study design? Not to perform conventional pharmacokinetic evaluations in this study?

2006

Pre-clinic

- Interaction with National Authorities
- FIH study

2018



*GLP: Good Laboratory Practices

Main Program peculiarity: straight in preterm neonates (N=40, 27-33⁺6wks GA)

The Learn Phase



Phase 2: proof of concept, multicenter, US study, double blind, randomized

CHF5633

56 patients

200mg/Kg
redosing 100mg/Kg

Curosurf

57 patients

2006

Pre-clinic

- Preterms with RDS
- Gestational age 24-29⁺⁶ weeks
- Endotracheal administration

- Interaction with National Authorities
- FIH study

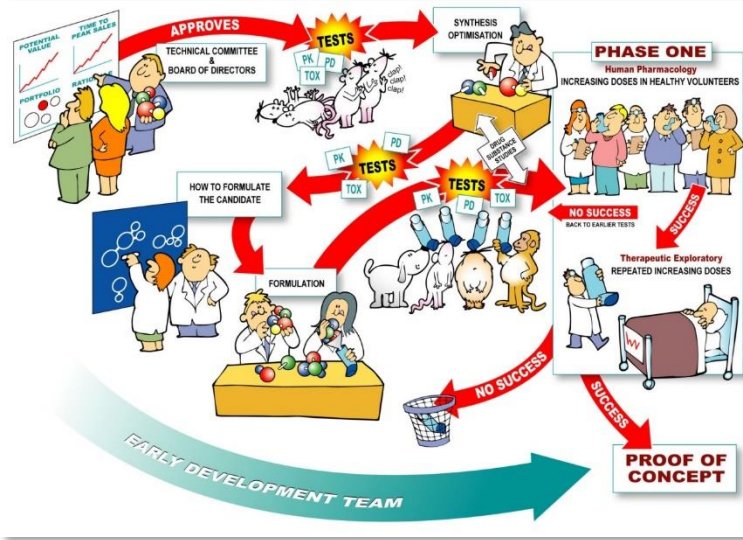
CHF5633 - good safety + efficacy profile, superimposable to Curosurf

No statistical difference between the two surfactants in terms:

- Reduction of oxygen requirement
- Incidence of BPD and mortality/BPD
- Re-dosing
- Adverse events

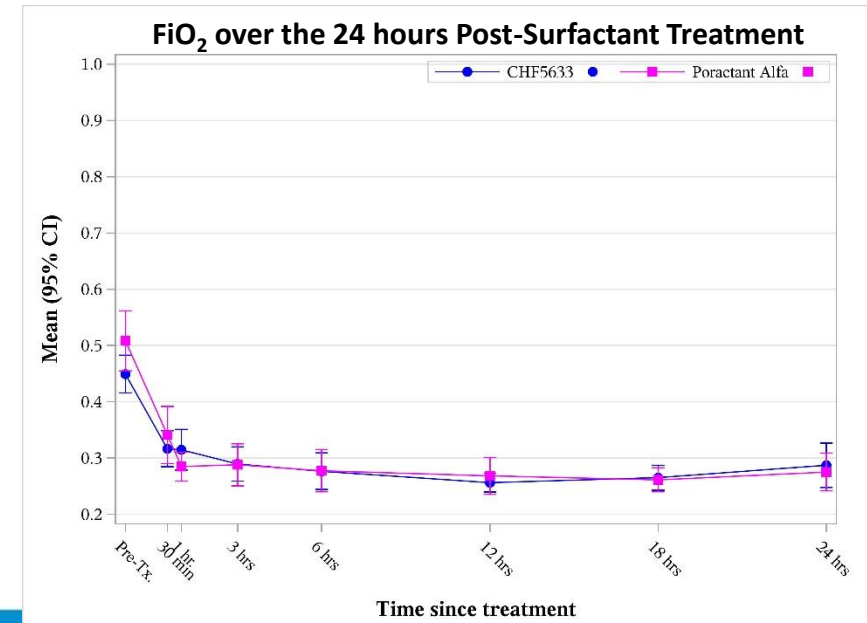
- Interaction with FDA and EMA
- POC ph2 study

2018



Therapeutic Efficacy in Patients

CLINICAL POC

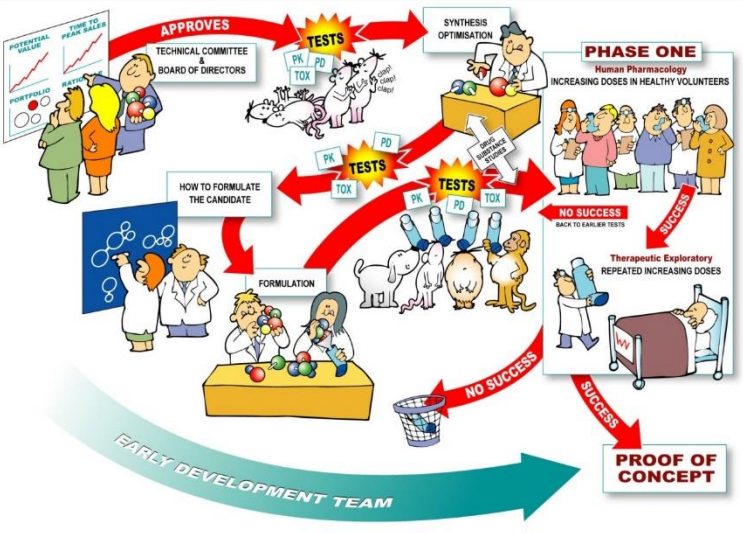


The Learn Phase



Interactions with FDA & EMA in 2014 - 2016

- ✓ FDA pre-IND meeting in September 2014
- Discussion on:
 - Adequacy of the drug product and drug substance specifications in the IND
 - Adequacy of the nonclinical package and the First-in-Human clinical study for initiating an IND with the proposed Phase 2 POC clinical study
 - Phase 2 POC clinical study design, comparator control, dose, target population, efficacy and safety variables, re-dosing criteria and biomarkers of inflammation evaluation
 - Rationale for using the outcome of the proposed clinical study to design the pivotal study



2006
Pre-clinic

- Interaction with National Authorities
- FIH study

- Interaction with FDA and EMA
- POC ph2 study

2018



Interactions with FDA & EMA in 2014 - 2016

✓ Submission and Approval (Nov 2016) of the Paediatric Investigational Plan (PIP) in EU

Content on:

- Adequacy of the drug product, drug substance, nonclinical package and the First-in-Human clinical data
- Clinical Plan:

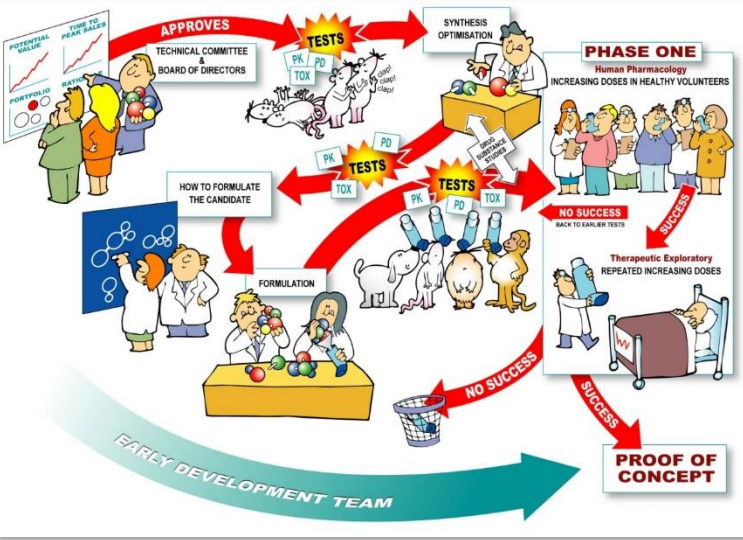
2006

Pre-clinic

- Interaction with National Authorities
- FIH study

- Interaction with FDA and EMA
- POC ph2 study

2018



TYPE OF STUDY / DESIGN	POPULATION	TREATMENT	ENDPOINTS
FIH Study Phase 1 multinational, multicentre, open label, single escalating dose, per-cohort	27 - 33 Week GA preterm neonates with clinical and radiological findings typical of RDS N=40	First cohort (A): CHF5633 1.25 mL/kg (100 mg/kg) in one single dose Second cohort (B): CHF5633 2.5 mL/kg (200 mg/kg) in one single dose	Short term and long term safety evaluations Explorative / no formal power calculation
POC Study Phase 2 multicentre, double blind, randomized, single dose, active-controlled	24 - 29 Week GA preterm neonates with RDS N = 63 Group 1 + 63 Group 2	Group 1: CHF5633 synthetic surfactant 2.5mL/kg (200 mg/kg) Group 2: Curosurf 2.5mL/kg (200 mg/kg) Group 1 and 2: re-dosing when needed at 1.25 mL/kg (100 mg/kg)	Short- term efficacy profile evaluation (O ₂ requirement and ventilatory support) Mid-term efficacy profile evaluation (incidence of BPD and death/BPD at 36 weeks PMA, mortality at 28 days and 36 weeks PMA, RDS-associated mortality through 14 days of age and other major co-morbidities of prematurity) Explorative / no formal power calculation
PIVOTAL Study Phase 3 multicentre, double blind, randomized, single dose, active-controlled, non-inferiority	24 - 33 Week GA preterm neonates with RDS N = 516 (to be refined after completion of POC study)	Group 1: CHF5633 synthetic surfactant 2.5mL/kg (200 mg/kg) Group 2: Curosurf 2.5mL/kg (200 mg/kg) Group 1 and 2: re-dosing when needed at 1.25 mL/kg (100 mg/kg)	Comparative short- term efficacy profile evaluation (O ₂ requirement and ventilatory support.using one of the short-term respiratory measurements evaluated in the POC study, e.g.FiO ₂ AUC0-12h)

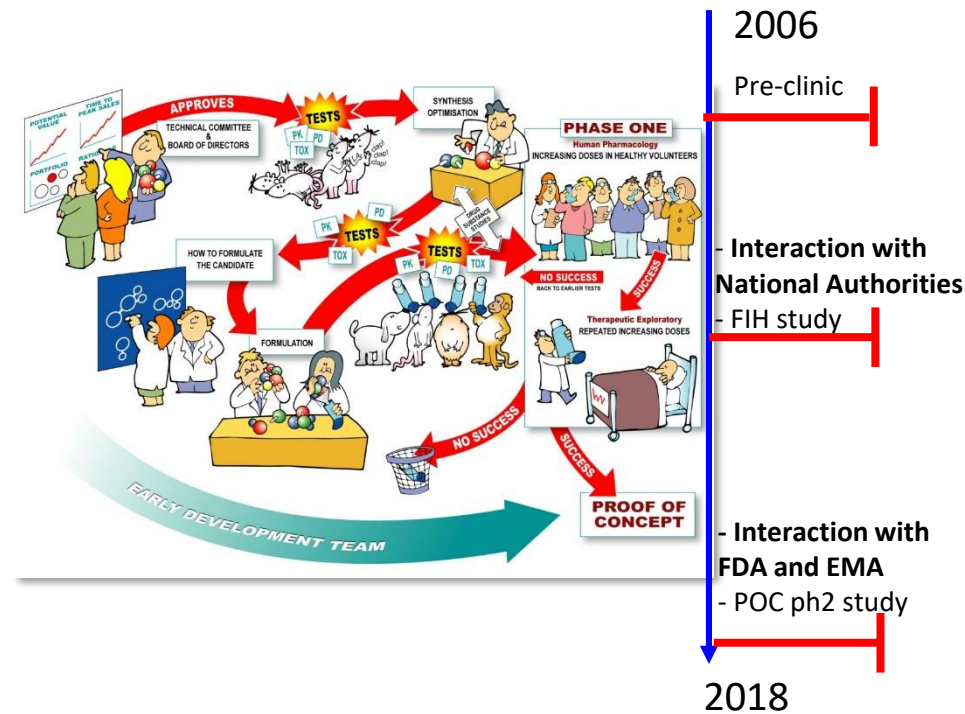
Therapeutic Efficacy in Patients

CLINICAL POC

The Learn Phase



FDA & EMA / EU National Agencies Opinions in comparison

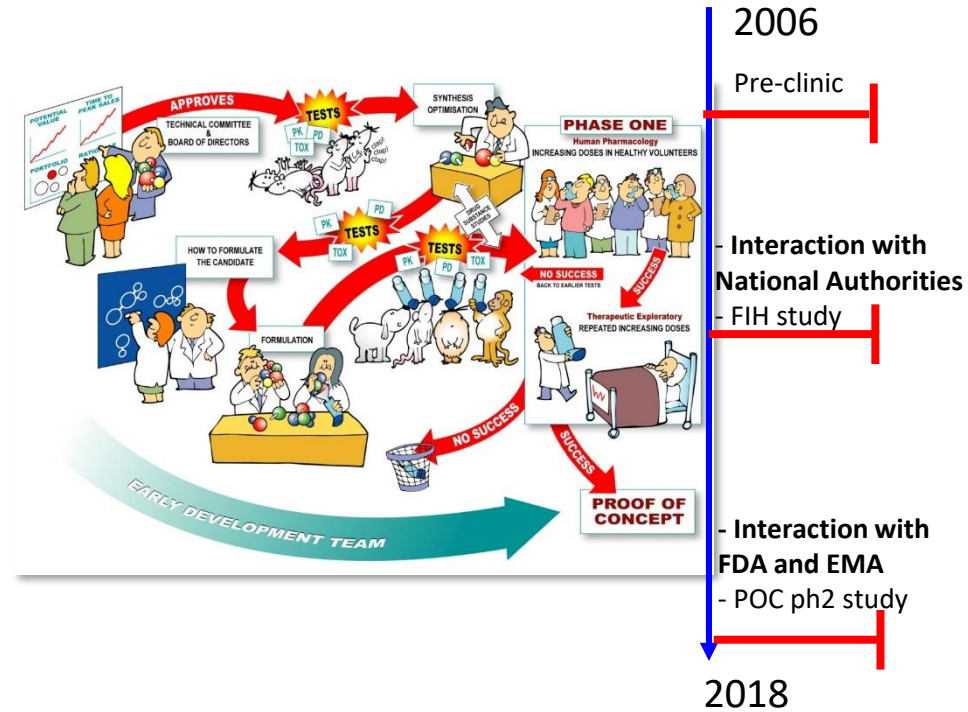


FDA	EMA /MHRA / BfArM
Request for additional non-clinical data for IND to support the maximum feasible dose and the clinical dosing in the POC study	Non-clinical package considered adequate for starting the clinical program
Request to evaluate the full range of neonatal age ranges. Or foreseen indication only in preterm neonates up to 33wks GA; since RDS due to surfactant deficiency is uncommon after approximately 33 wks GA while other causes of respiratory failure are more common above this age range	Accepted the plan and the possible indication in all preterm neonates of less than 37 wks GA; no age limitation
Request to include in phase 2 and 3 trials primary endpoints consistent with those used for development of previous surfactants, including mortality and BPD Accepted PD oxygenation parameters for POC study but request for an end-of-phase 2 meeting to discuss the phase 3 clinical program mainly in terms of selected primary endpoint A single pivotal trial may not be sufficient unless the trial is very large and meets the criteria for a single study to support efficacy	Accepted PD oxygenation parameters, ventilation (type, values, lung ultrasound, pre-and post-surfactant X-ray) prior to and after surfactant application Inclusion of BPD as secondary endpoint is acceptable for both phase II and III trials
Include an evaluation of immunogenicity in all planned clinical trials at least in a subset of patients	Assessment of immunogenicity does not seem required in view of the immature immune system of premature neonates, also in light of an optimised handling approach and reducing the iatrogenic blood loss this must be scientifically justified Suggestion to avoid the test in phase 3

The Learn Phase



The Learn Phase is devoted to establish the so-called “proof of concept” (POC = Evidence of Clinical Safety and Efficacy)

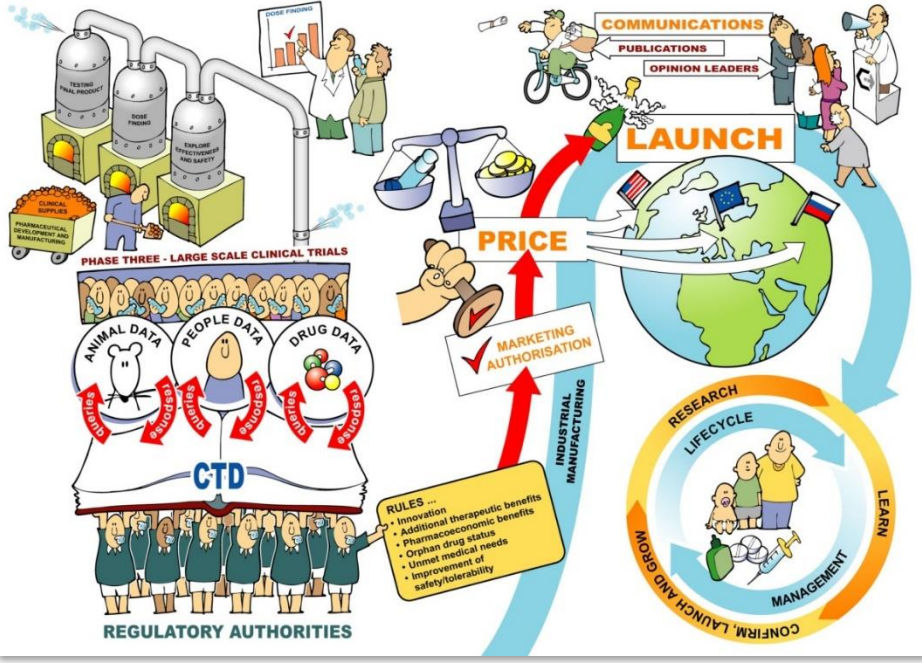


BUDGET *including labour costs*



Total for Learn Phase: 42 M
 FIH Study: 3 M
 POC Study: 8.2 M

Confirm, Launch & Grow Phase



2018

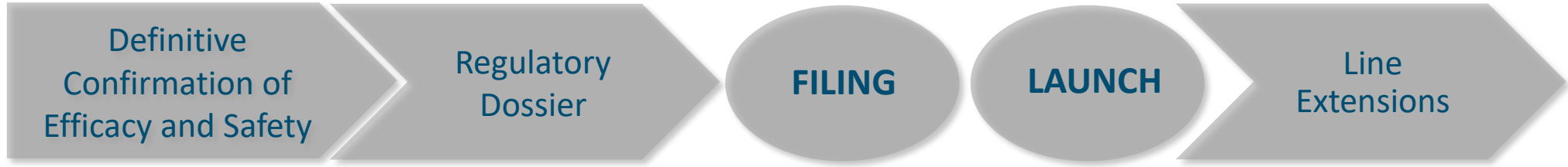
The Confirm, Launch and Grow Phase is devoted to complete the clinical development (pivotal studies) and to produce a regulatory dossier necessary to achieve marketing authorization / then to expand the use in all indications and patient populations of interest

Chiesi Corporate /Affiliates Ongoing Discussion on CHF5633 Future

Having 2 surfactants (synthetic and animal derived) with similar profile!!

Positioning vs Curosurf® in nRDS
taking into account local markets needs / cost of production and potential price

Alternative indications
where an unmet need is present (e.g. ARDS)



Lesson Learnt from this Experience - Conclusions

At Project Level

- Suggested interactions with Regulators as soon as possible
- More specific regulatory guidances are needed
- Partial discrepancy between FDA and EMA/EU National opinions
- Standard product development in other therapeutic areas are not applicable in neonatology
- Need to design a product development for each population subset/ each neonatal pathology

At Clinical Study Protocol Level

- Need for:
 - ✓ standardization of requested measurements in each investigational site
 - ✓ well defined primary endpoint and acceptable by regulators limiting the sample size
 - ✓ reducing the number of secondary endpoints and data to be collected
 - ✓ enhancing the adverse events reporting
 - ✓ education in neonatology among stakeholders

Membership & collaboration with INC is a chance for solutions





International Neonatal Consortium







International Neonatal Consortium

Session II: Harnessing the Science

Christina Bucci-Rechtweg (Novartis), Chair



1:00 p.m. – 1:05 p.m. Welcome - Joseph Scheeren, President and CEO, Critical Path Institute

1:05 - 1:15 p.m. INC at Four Years: Neonatal Growth and Predicted Long-Term Outcomes

SUSAN MCCUNE, DIRECTOR, OFFICE OF PEDIATRIC THERAPEUTICS, FDA

1:15 p.m. – 2:30 p.m. *Educating the Neonatology Community on the Drug Development Process*, RON PORTMAN

Session I: Setting the Scene, Gerri Baer (OC/FDA), Chair

- Panel: Robert Ward (U-Utah), Susan McCune (OC/FDA), Laura Fabbri (Chiesi)

2:30 p.m. – 3:00 p.m. Coffee Break

3:00 p.m. – 4:25p.m.

Session II: Harnessing the Science, Christina Bucci-Rechtweg (Novartis), Chair

- **PANEL: NORMAN BARTON (Takeda), CHRIS MILNE (Tufts CSDD), THOMAS MILLER (BAYER)**

4:25 p.m. – 5:30 p.m.

Session III: Addressing Neonatal Needs within the Current Environment, ED CONNOR (I-ACT for Children), CHAIR

- **PANEL: SUSAN MCCUNE (OC/FDA), AGNES KLEIN (HEALTH CANADA), APRILE PILON (Trove Therapeutics), MARY SHORT (Lilly), MARK TURNER (U- Liverpool), JENNIFER DEGL (Speaking for Moms and Babies, Inc), ANNE ZAJICEK (NIH/OD), KELLE MOLEY (MARCH OF DIMES), JAMES BAUMBERGER (AAP)**



International Neonatal Consortium

Innovation and the Drug Development Cycle Process and Players

Norman W Barton

Global Head Clinical Sciences

Rare Genetic and Immunologic Disorders and Neonatology

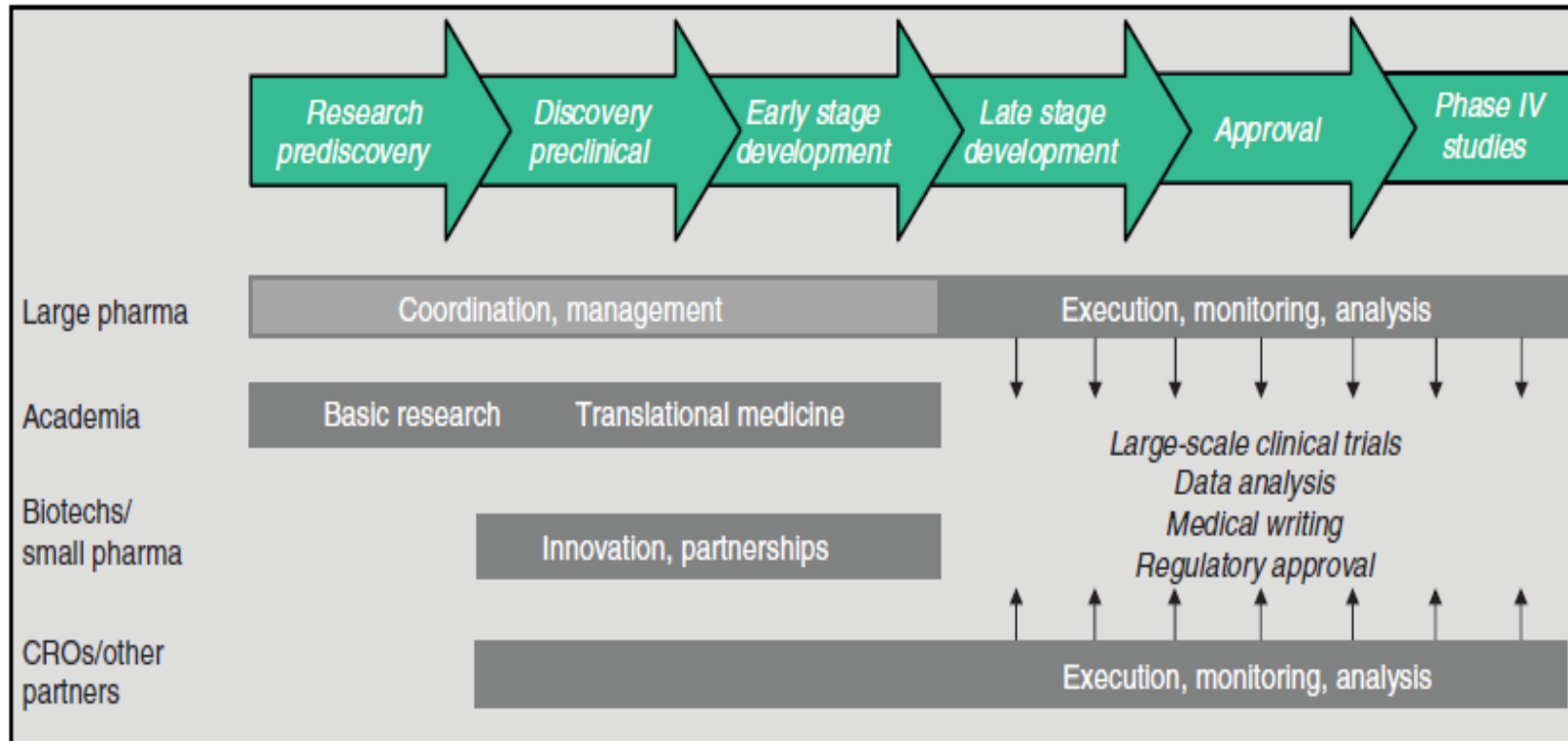
Takeda R&D Boston MA



The R&D Ecosystem Overview

- Drug development is a complex evolutionary process in which the fittest candidates survive
 - A costly marathon that requires commitment and endurance: >2B and >10 years
- Innovation networks focused on core competencies collaborate to address 3 key challenges
 - Cycle times for knowledge/evidence generation
 - Capital requirements...the further you go the more you need
 - Risk mitigation
- Vertical integration is a thing of the past

The R&D Ecosystem: Overview



The R&D Ecosystem: Process

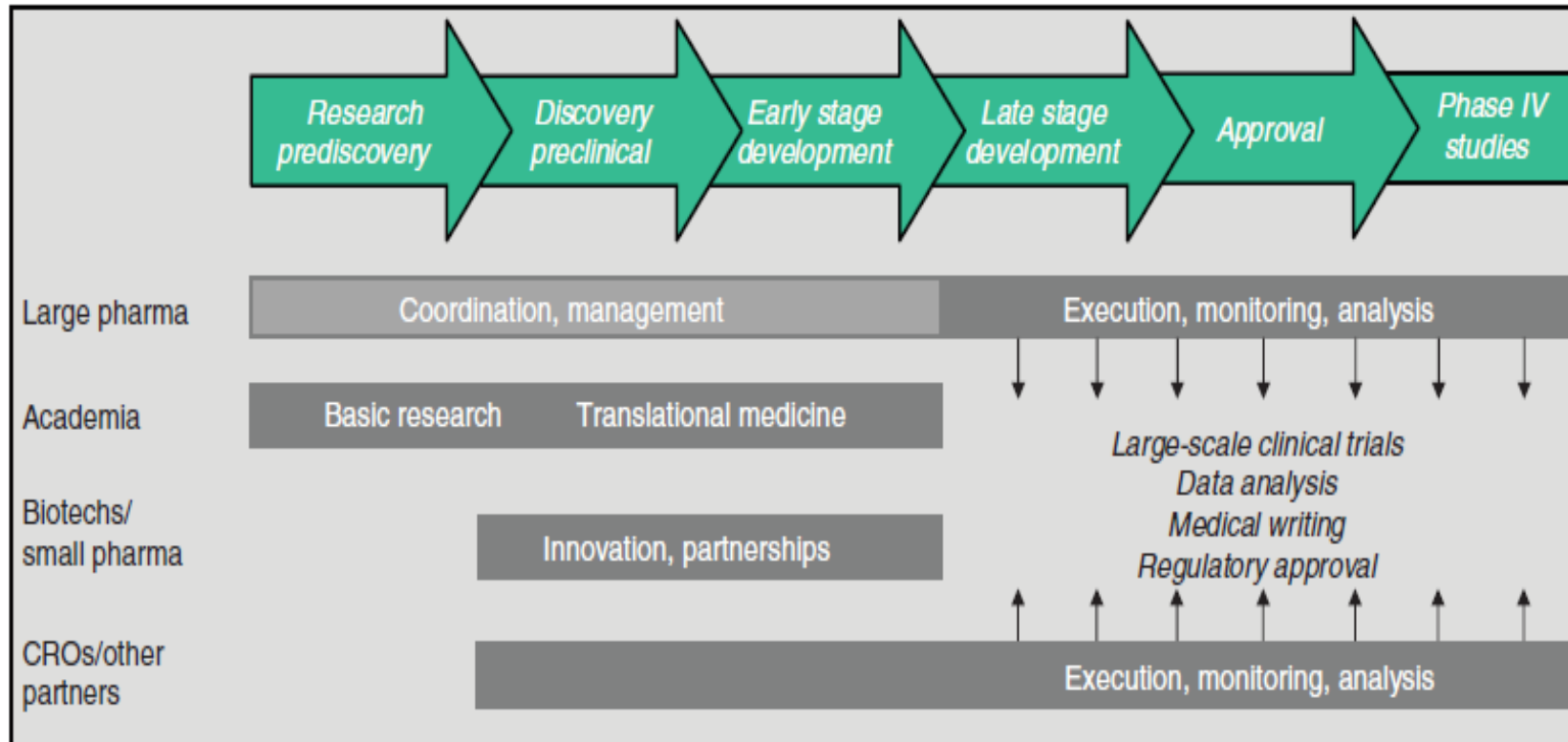
- Basic Research and Drug Discovery
 - Goal- identify a druggable molecular target that is causally related to the disease process
 - For small molecules optimized pharmaceutical properties (adsorption, distribution, metabolism and excretion) and lack of overt toxicity are critical attributes
 - For biologics appropriate methods to deliver the compound to the molecular target are essential
 - Need to demonstrate a meaningful biological effect in a relevant model of the disease process; a strong scientific rationale is needed to progress the compound into development
- Preclinical Development
 - Scale up GMP production of drug substance
 - Develop appropriate formulations for clinical trials
 - Execute toxicology program under GLP conditions

- Clinical development in preterm and term neonates
 - Assume data are available from studies in adults and children
 - Phase 1 pharmacokinetic studies to define dosing schedule and route of administration
 - Phase 2 pharmacodynamic studies to define doses that perturb markers of disease activity
 - Phase 3 registrational trials
 - Safety safety safety throughout

Challenges in Neonatal Drug Development

- Disease processes disrupt developmental biology that is unique to preterm or term newborns; there are no adult counterparts
 - Mechanistic/molecular understanding of disease process often limited
- Relevant preterm translational animal models suitable for proof of concept studies with drug candidate are frequently not available
- Drug product formulations suitable for neonatal trials require great attention with regard to volume, product concentration, excipients and compatibility with other co-administered drugs
- Biomarkers that inform dose selection and endpoints suitable for proof of efficacy are not defined for first in class products
 - Multiple data driven discussions based on the biology and pathophysiology of the disease process are required to reach agreement with regulatory authorities on informative markers and endpoints
 - Efficacy endpoints for regulatory decision making must capture whether the neonate survives and how (s)he feels or functions over time
- Outcomes suitable for product registration may not be determined until 1 or 2 years of life (corrected age) often with the need for follow up into late childhood

The R&D Ecosystem: Players



Players in the Innovation Network

- Academia
 - Strong basic research and translational capabilities
 - Deep disease expertise
- Small Pharma/Biotechs
 - Focus on emerging technologies
 - Live or die on a single platform or asset
 - Highly innovative R&D
- Large Pharma
 - Focused product development teams with deep functional expertise
 - Provide resources and investment
 - Regulatory and manufacturing expertise
 - Capable of executing large scale global trials
 - Global regulatory, sales and marketing capabilities

Partnering organizations	Strengths	Weaknesses
Big pharma	Strong drug R&D expertise; strong regulatory affairs; strong project management; strong marketing; internal resources for projects	Bureaucracy: slow decisions; a culture of controlling R&D collaboration
Small pharma/ biotech	Specific drug R&D expertise; flexibility of decision making	Drug R&D expertise not complete; market knowledge often limited; often lack internal resources for projects
Academia	Strong basic research: biology/ genomics, target identification/ validation; understand disease and can think 'out of box'	Drug R&D expertise limited; desire to publish early can conflict with patenting; not used to project management; limited commercial understanding

What does it take to succeed?

- A clearly communicated vision for value creation
- Talented researchers with passion
- Motivated groups of people with purpose and tenacity

Reasons to be Optimistic

- Accelerated approval provisions available to FDA and EMA sometimes allow early introduction of therapies with strong data packages in the context of large unmet medical need
- Venture capital firms are beginning to look seriously at the unmet needs of neonates

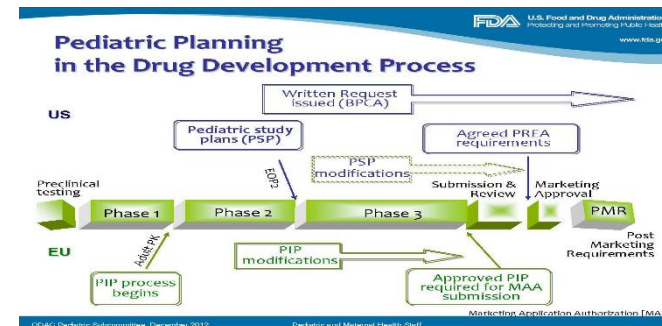
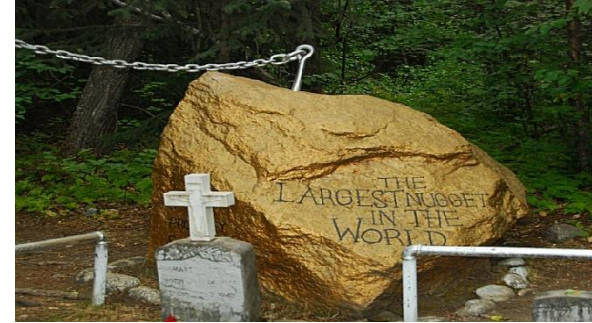
New Day for an Old Problem

**Christopher-Paul Milne
DVM, MPH, JD**

**INC Symposium
Bethesda, Maryland
May 1, 2019**

Agenda

- Industry under Barrage, not Buried under
- The Bad, Good News
- What Works...for a New Day!





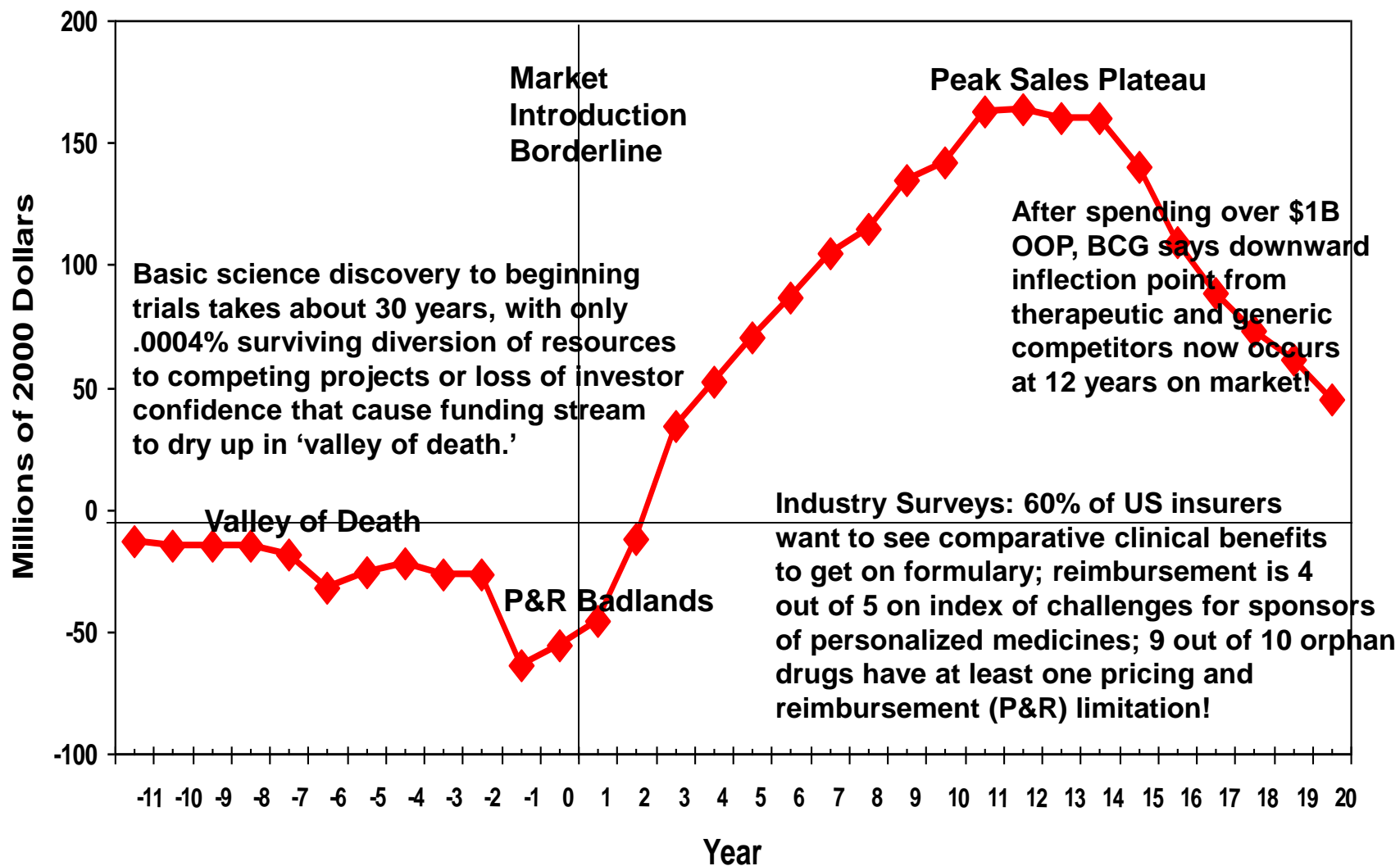
Lessons Learned from History...or Not!

In early 1900s' Alaska, during the Klondike Gold Rush...

- 100,000 prospectors left home
- 40,000 actually made it there
- 20,000 set up mining operations
- 300 struck it rich (>\$15,000)
- 50 kept their “fortunes”

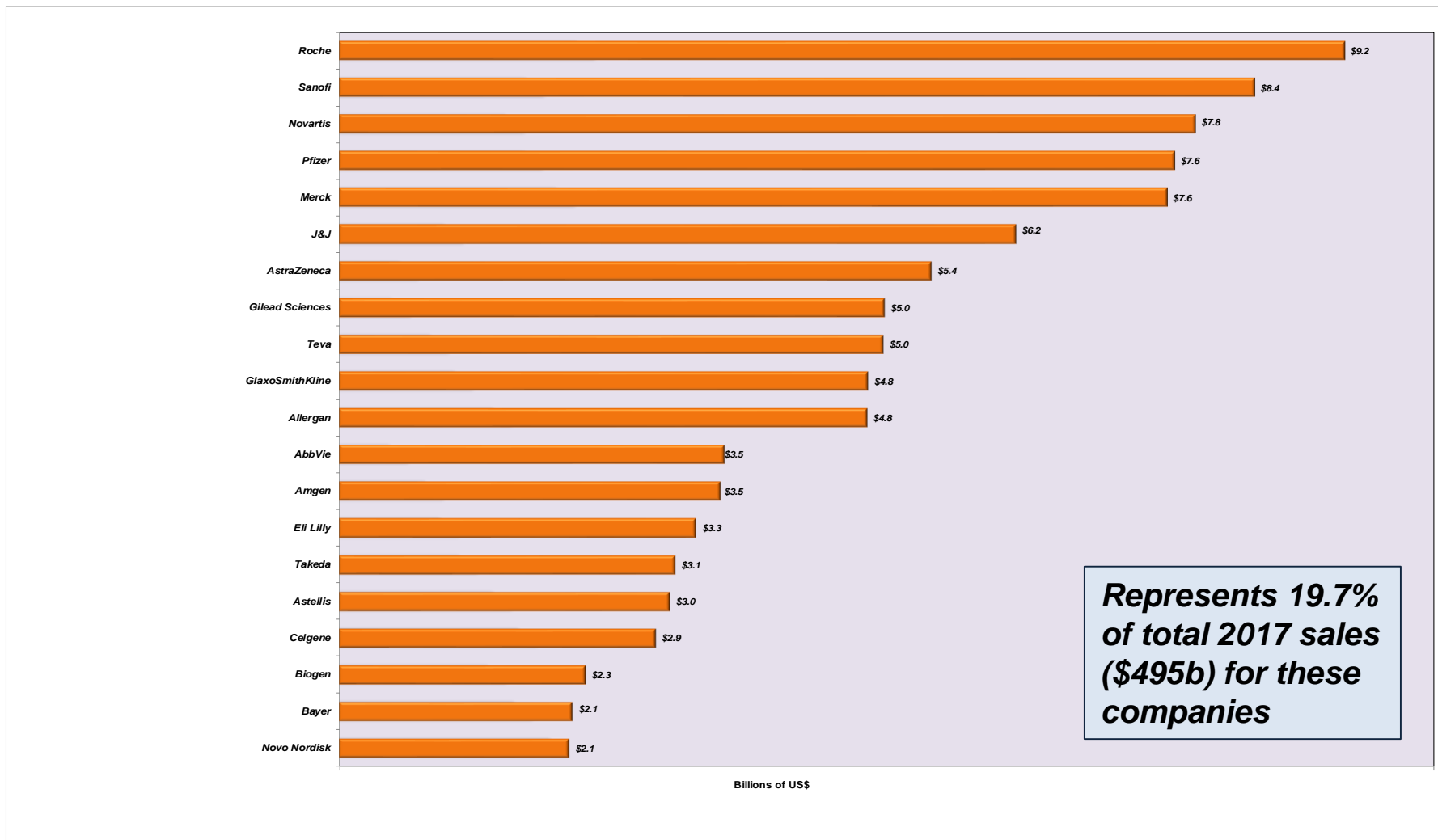
Odds of success were 5 in 10,000...about the same as getting a “new” drug to market!

Cash Flows over Product Lifecycle



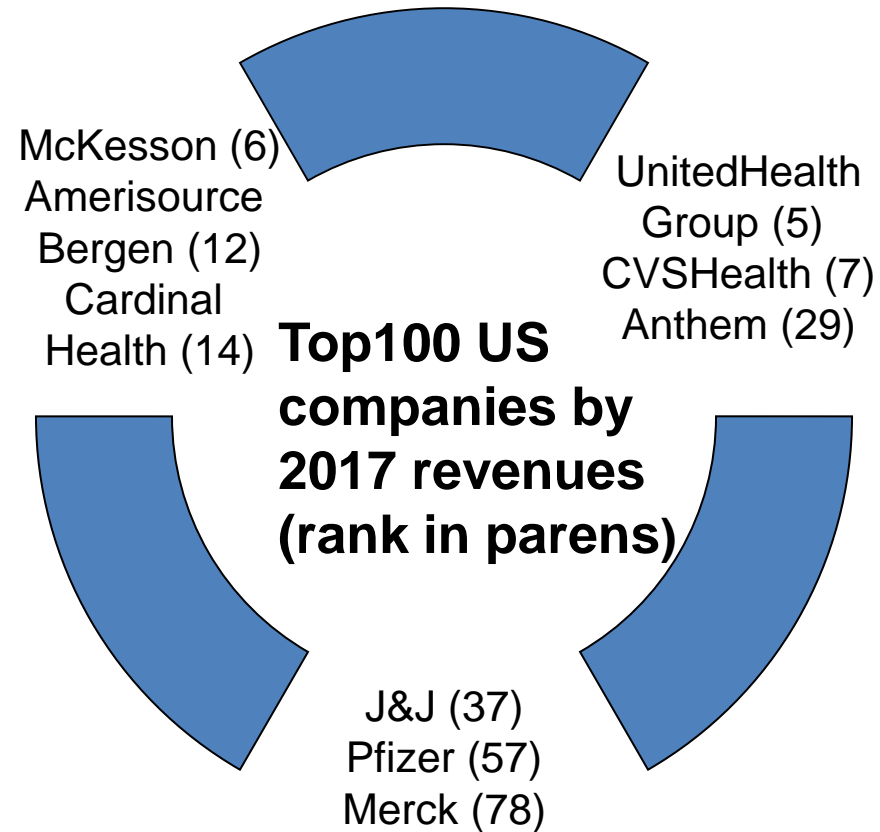
(Source: Grabowski, Vernon, & DiMasi. *Pharmacoeconomics* 2002; 20 Suppl. 3: 11-29)

Top 20 Companies Spent \$97.5B in Pharma R&D in 2017



Source: Pharmaceutical Executive, June 2018

So who's making money on Rx drugs...perhaps not who you think?

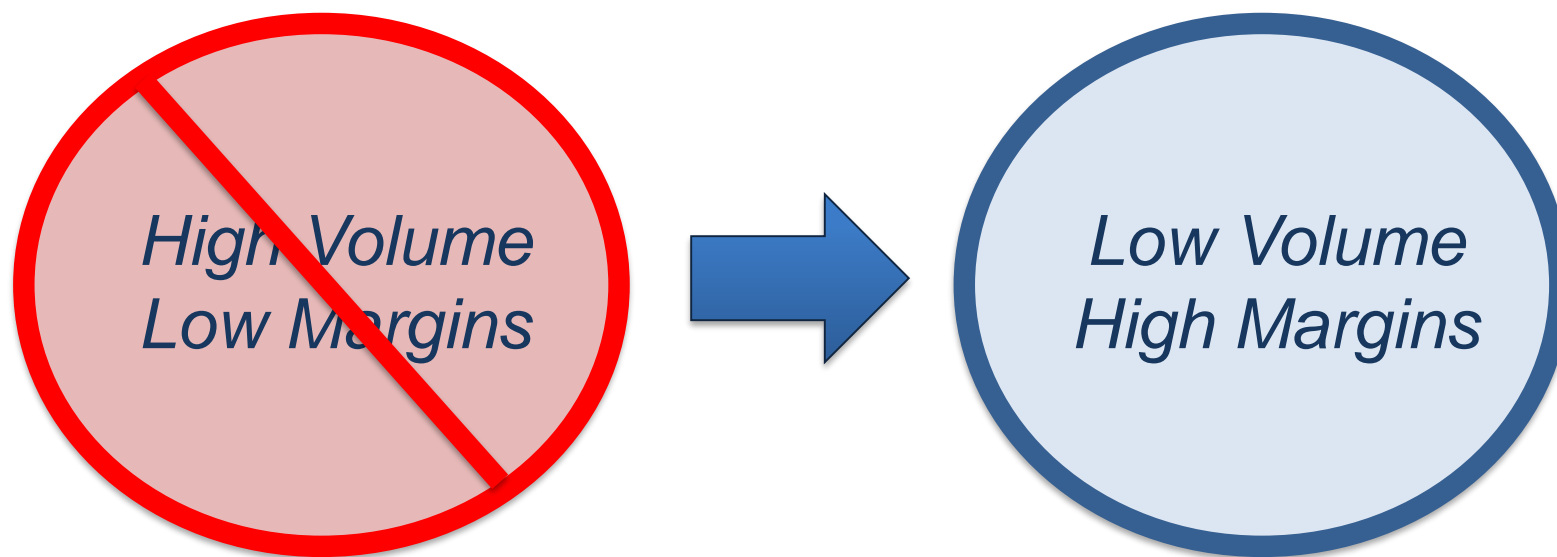


Same Question, Different Perspective: ROI versus Revenue

Return on Invested Capital 2017
Novo Nordisk – 80%
Facebook – 24%
Apple – 22%
Regeneron – 21%
Microsoft – 18%
AbbVie – 14%
Biogen – 14%
Celgene – 14%
Alphabet – 8%
Amazon – 7%

Source: Bill Trombetta, Industry Audit, Sept 2018, www.pharmexec.com

How are they doing it? The “New” Pharma Business Model!



Deloitte 2018 reports top 12 pharmacos expected ROI of only 1.9%, lowest since metric instituted in 2010; but SMEs will achieve ROI of 9.3% by focusing on high value products for unmet medical needs.

***Precision Medicines
Orphan Drugs
Specialty Pharma***

Source: Tufts CSDD, 2016

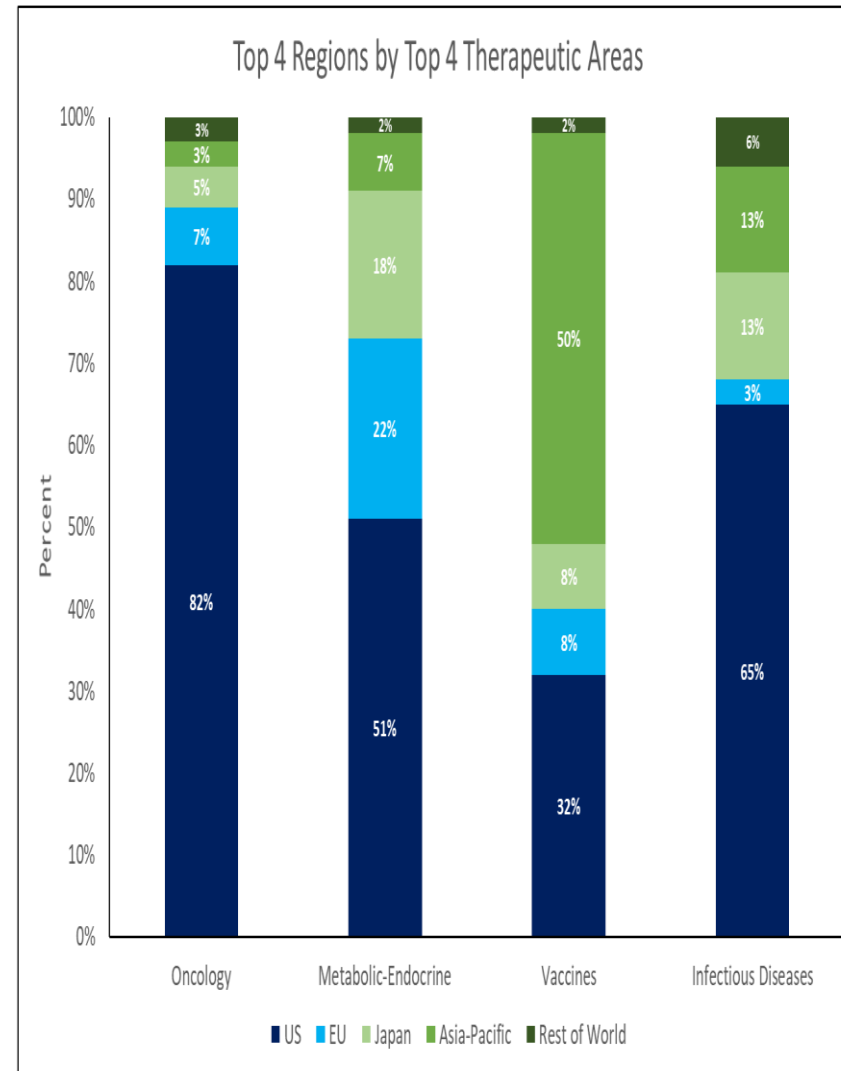
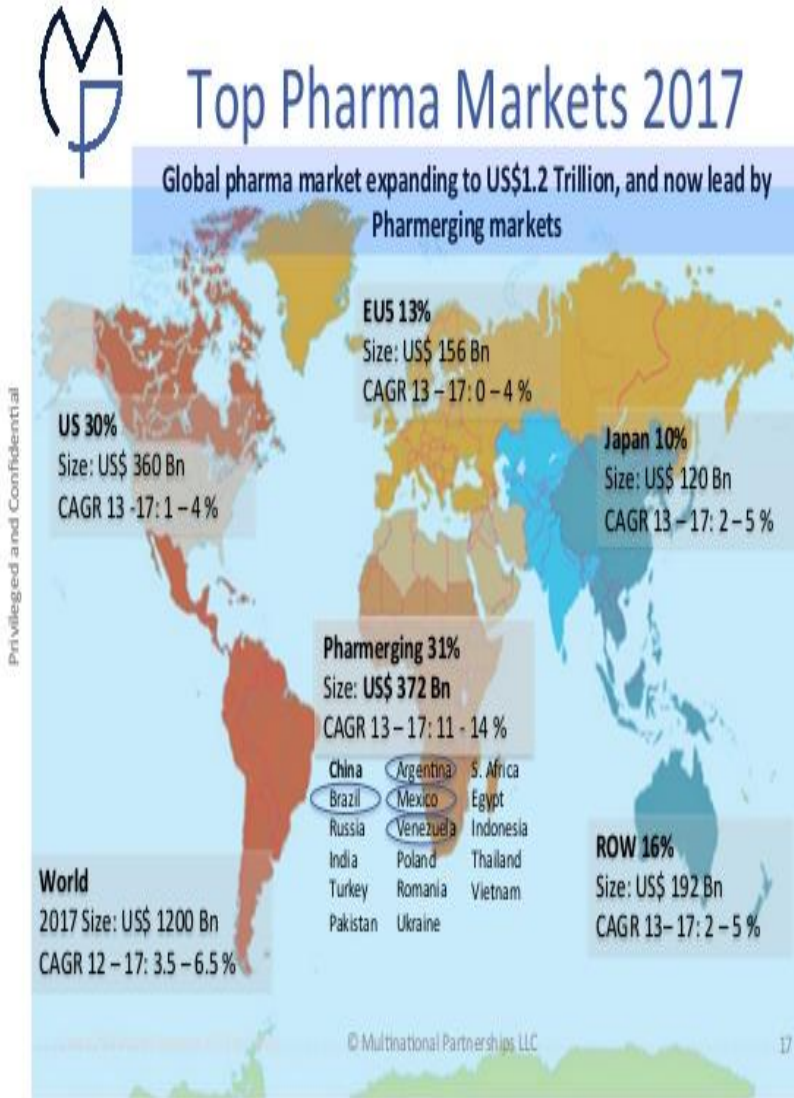
The Bad, Good News!



Neonatal Mortality: Global Health Crisis

- ❖ Global toll:
 - Neonatal period accounts for 40% of all deaths of children under 5 (over 3M in 2010)
 - Average daily mortality during neonatal period is 30x higher than post-natal period
 - Of 15M pre-term births in 2010, 1M died (WHO 2012 Update on Neonatal Conditions)
- ❖ Global death ranks for Neonatal Encephalopathy and Neonatal Sepsis decline from 17th and 20th in 1990 to 24th and 25th, respectively, in 2010 (Global Burden of Disease Study 2010, Rafael Lozano et al, The Lancet Dec 15/22/29 2012; 380: 2095 et seq)
- ❖ US has 66% more neonatal deaths than comparable OECD country average; even recent 13% decrease in US mortality rate was eclipsed by 23% decrease in comparator countries (Kamal & Gonzales, Infant Mortality in US, Kaiser family Foundation in 2015)
- ❖ Perinatal Conditions ranked 4th place in number of drug clinical trials worldwide (152 w/180k patients) over 6.5 years, but ranks 2nd in DALYs (Bourgeois FT, Olson KL, Mandl KD. Association between pediatric clinical trials and global burden of disease, Pediatrics AAP 2014)

Emerging Markets: Doing Well by Doing Right!



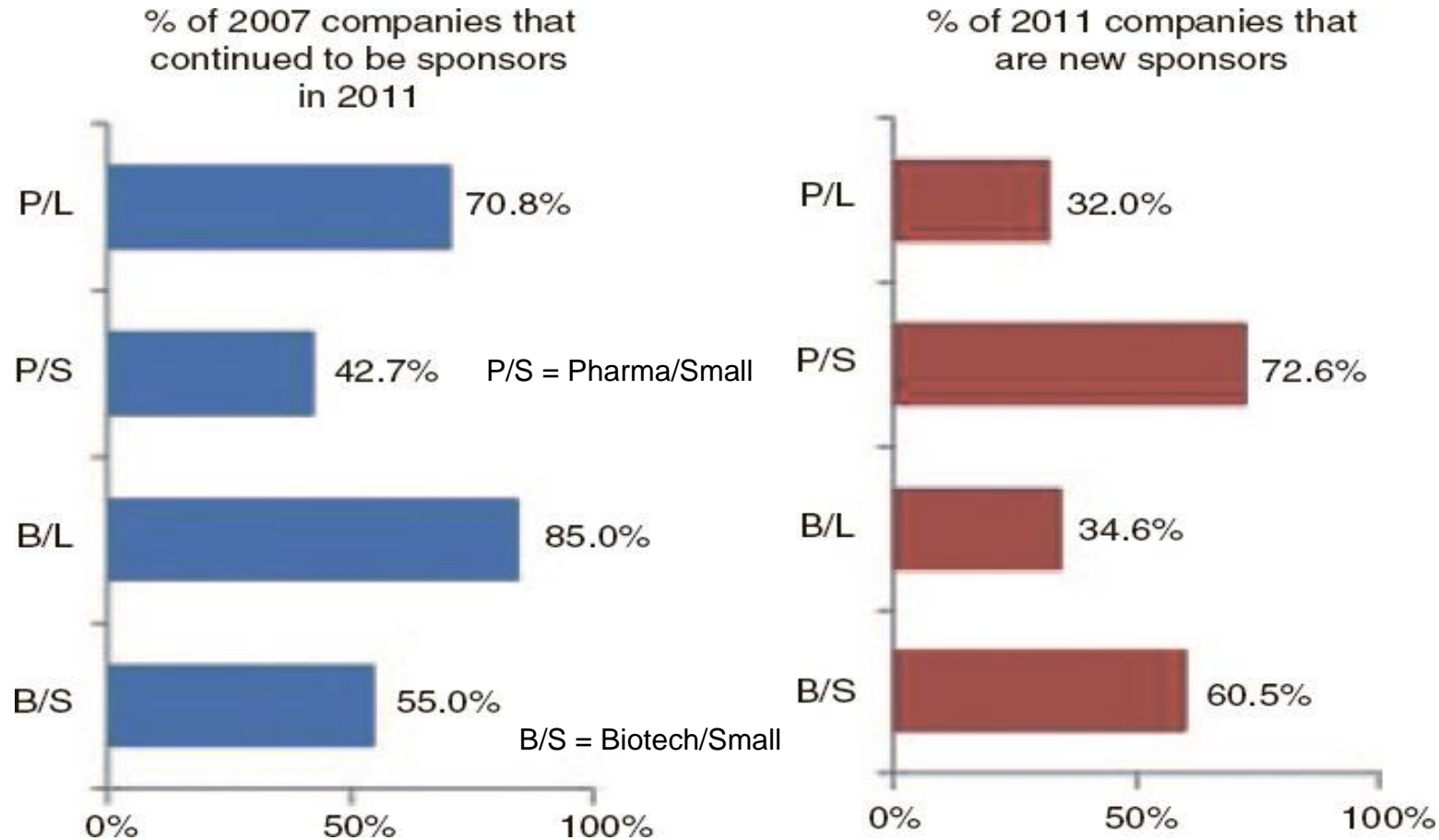
Emerging Markets are future for Big Pharma. Neonates are EMs' future, ranking 4th in WHO Public Health Priority List. Goodwill is still a good reason to do some things that benefit more than the bottom line!

Challenging environment for orphan drugs not dissimilar to neonates

Type of Orphan Challenge	% of Drug Programs Encountering
Variability in expression, severity, or course of ds.	76%
Geographically dispersed patient population	72%
Very small patient pop.	61%
Selecting among multiple development pathways	61%
Lack of endpoints, etc.	43%

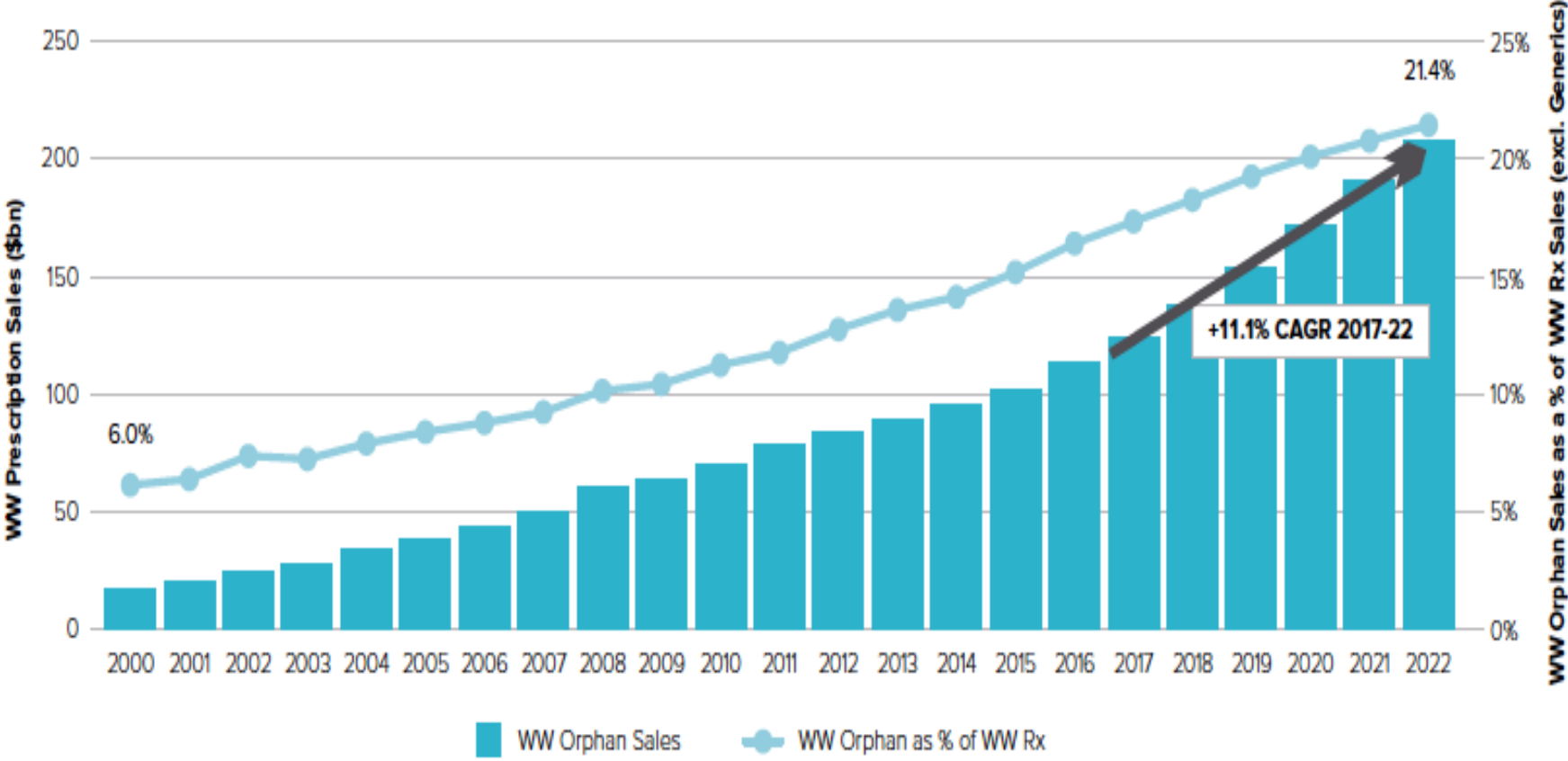
Source: Tufts CSDD Impact Report, v.20, #3; May/June 2018

Emerging sponsors rapidly populate and de-populate orphan drug field



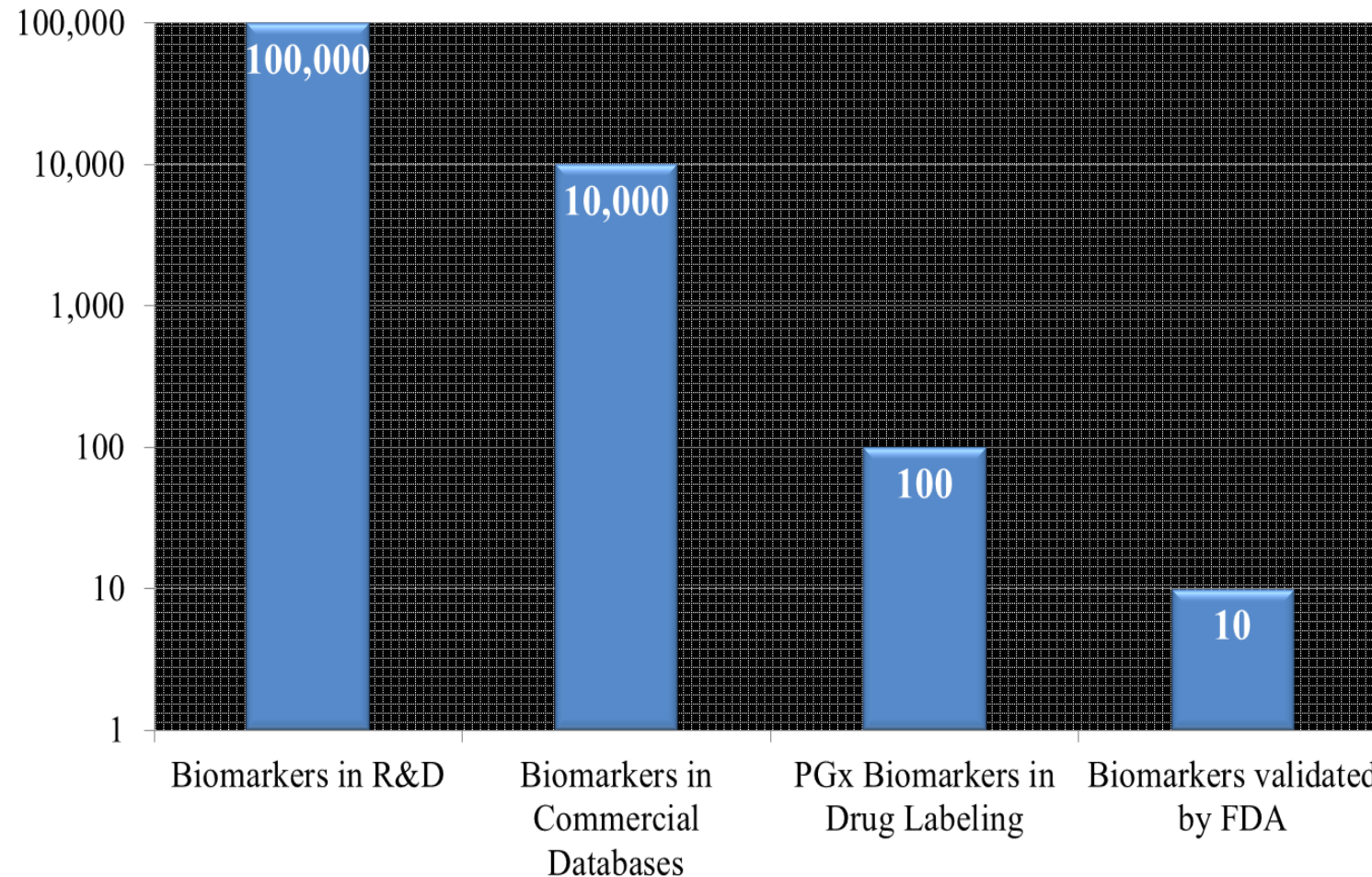
An “emerging sponsor” is not an holder of any previously approved NDA/BLA applications. Recently, as many as 40% of “new” drugs were from emerging sponsors, who share many of the same characteristics as start-ups or small companies with little or no experience getting products to market. Pharmaprojects 2017 report: of 4,000 pharma firms with active pipelines, 56% have just one or two products in pipeline.

Worldwide Orphan Drug Sales & Share of Prescription Drug Market, 2000-22



Source: EvaluatePharma® (Feb 2017)

Emerging technology (eg.,biomarkers) is advancing development science, but regulatory science challenge is exponential!



Despite 29 submissions, only 8 surrogate endpoints fully qualified. Some industry comments on draft FDA Guidance complain about lack of clear, predictable and specific regulatory framework that lays out type and level of evidence supporting regulatory decision-making. FDA published list of SEs that were primary endpoints for approvals to 'modernize' clinical trials along with advancing master protocols, natural history models, and RWE.

Emerging health crises, sometimes...it's just a tough go!

Virus or bacteria	Year cause discovered	Year vaccine licensed	Years elapsed
Typhoid	1884	1989	105
Haemophilus Influenzae	1889	1981	92
Malaria	1893	None	–
Pertussis	1906	1995	89
Polio	1908	1955	47
Measles	1953	1995	42
Hepatitis B	1965	1981	16
Rotavirus	1973	1998	25
HPV	1974	2007	33
HIV	1983	None	–

Source: AVAC, May 2014

Industry self-evaluation of progress on pediatric development challenges: 2008-2016

Source: Tufts CSDD Impact Report; v.18, #6: Nov/Dec 2016

Research Challenge	Good but still a work in progress	Slow but moving in the right direction	Negligible
Neonatal studies	9%	27%	64%
Age-appropriate formulations	36%	45%	18%
Rare diseases in children (e.g., oncology)	18%	55%	27%

❖ Over 500 PREA/ BPCA pediatric studies in just over 15 years, only 43 include neonates, with few contributing clinically useful information, meanwhile we're spending \$30B per year to counteract impacts of pre-maturity (Chen et al, 2019)

What Works for a New Day?

Advocacy:

Platform off existing programs or legislative proposals: Pediatric PRV, Pediatric Formulation Task Force, Breakthrough Therapy Designation

Incentives:

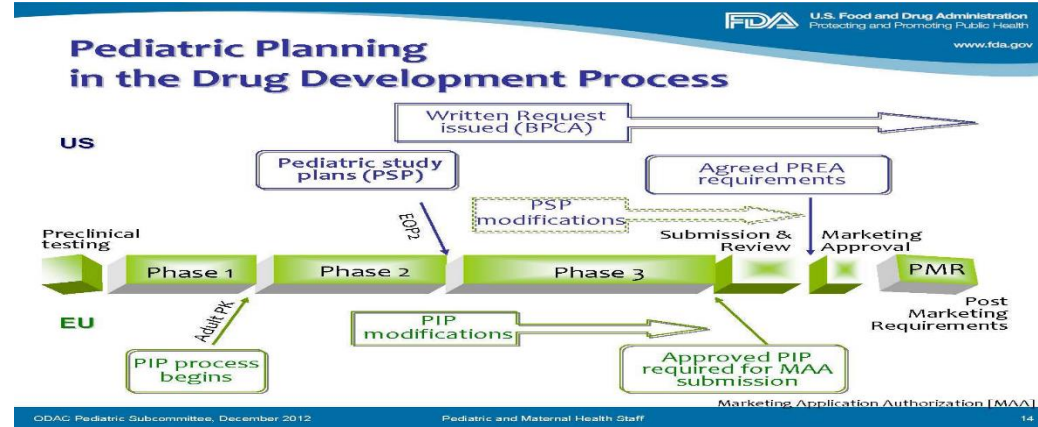
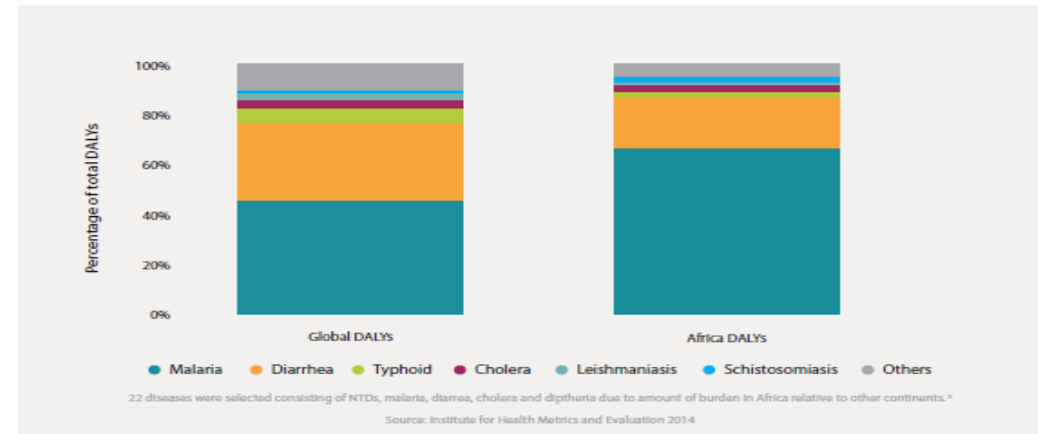


Figure 1: Proportion of neglected tropical diseases



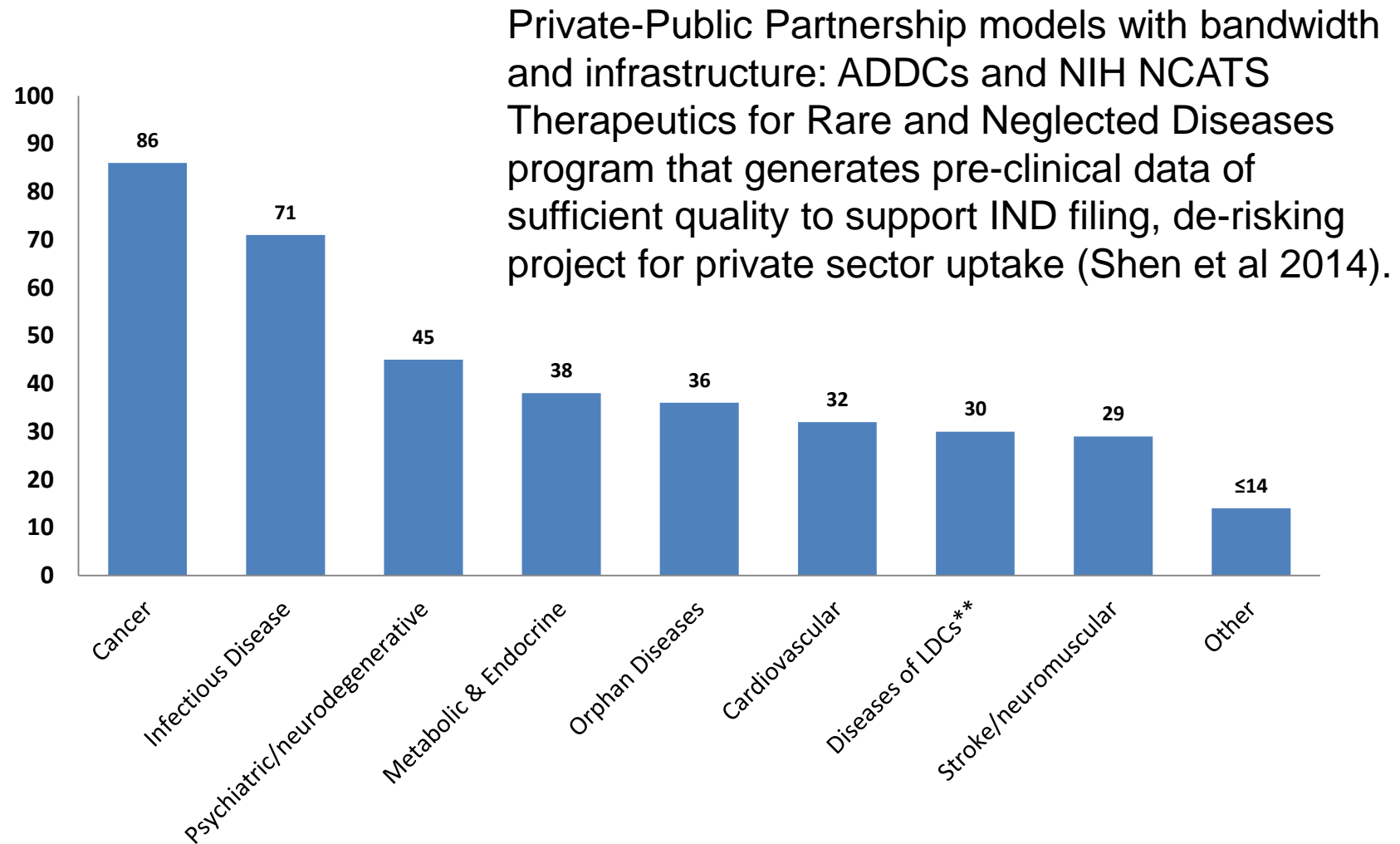
Public-Private Partnerships:

PREA/BPCA Incentive: Still a Work in Progress

Goals	A great deal	Good but still a work in progress	Slow but moving in right direction	Negligible
Increasing availability of age-appropriate formulations	0	18%	55%	27%
Increasing pediatric dosing info in labels	0	64%	36%	0
Pediatric studies an integral, routine part of drug development	36%	27%	36%	0
Increasing access to pediatric expertise within biopharma companies	9%	55%	36%	0
Increasing pediatric expertise within FDA	36%	36%	27%	0

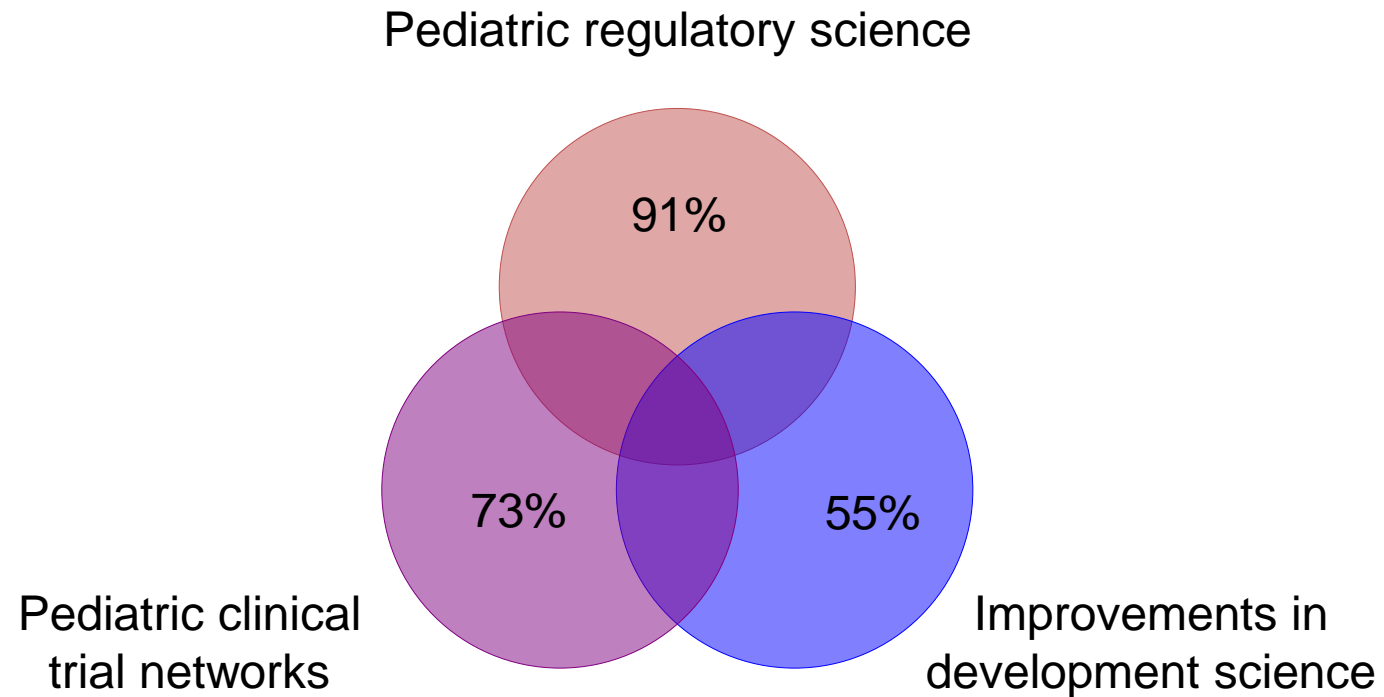
Source: Tufts CSDD Impact Report; v.18, #6: Nov/Dec 2016

Percent of Academic Drug Discovery Centers (ADDCs) Focused on Particular Therapeutic Areas



Source: Frye, S., Crosby, M., Edwards, T., & Juliano, R. (2011). US academic drug discovery. *Nat Rev Drug Discov*, 10(6), 409-410. doi:10.1038/nrd3462; ** LDCs = less developed countries

What industry believes will work!



Source: Tufts CSDD Impact Report; v.18, #6: Nov/Dec 2016

Thanks for your Attention!





International Neonatal Consortium

How Do Life Science Companies Make Portfolio Decisions?

Implications for Pediatric / Neonatal Clinical Development Programs

Thomas F. Miller
VP & Global Head Pediatric Development
Bayer AG



Presentation Overview

- A look ‘behind the curtain’
- Defining value
- The *numerator*
- The *denominator*
- Other considerations
- Decision making in large vs. small companies
- Potential implications for pediatric / neonatal Rx development programs



A look ‘behind the curtain’

- Approaching a company with an ‘ask’
 - Changes in recent years
 - Grant portals / compliance
 - No single decision maker
- Many opinions regarding portfolio investment prioritization
 - Implications can be significant for insiders
 - Rotation in/out of therapeutic areas of focus at companies is to be expected over time
- Most (large, multi-national) companies use a common, quantifiable definition of ‘Value’ to minimize (but not fully eliminate!) individual bias relating to funding decisions

How Do We Define 'Value'?

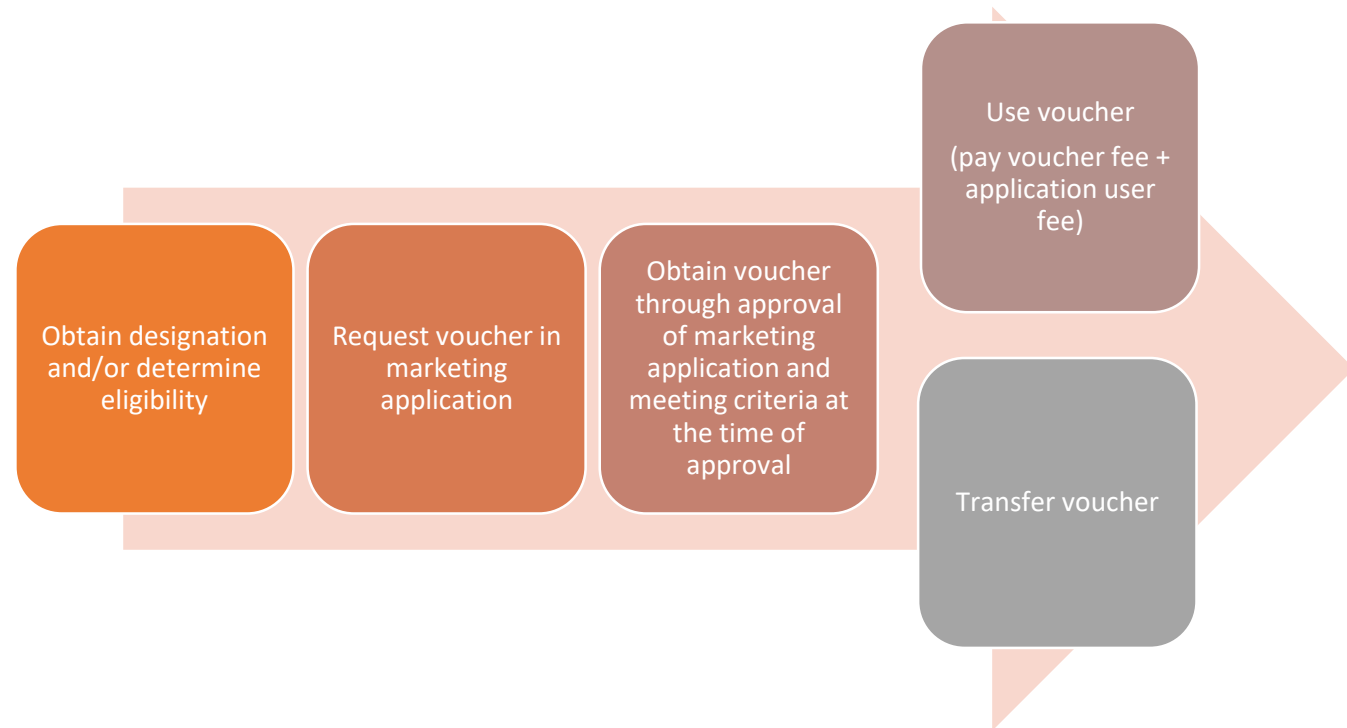
- Return on Investment (ROI) -- colloquial term
- Risk Adjusted Net Present Value (NPV) – primary industry assessment
 - Quantitative prioritization
 - Calculated as a fraction – considers *drivers* and *detractors* of value
 - Avoids 'pet project' advancement (theoretically!)

Defining Value: The ‘Numerator’

- Essentially, the *value drivers*
- Future revenues = sales over life cycle of Rx prior to exclusivity lapse
- Societal Impact / social venturing – rising importance to many companies
- Regulatory Incentives
 - Priority reviews – Fast Track (FDA), Breakthrough (FDA), PRIME (EMA)
 - Orphan designation
 - Rare Pediatric Disease Designation/Access to Priority Review Voucher

Rare Pediatric Disease Designation

- Addressed (again) in the **21st Century Cures** legislation -- which requires that:
 - (A) The ***disease primarily affects*** individuals aged from birth to 18 years...
 - (B) The disease is a serious or life-threatening disease in which ***the serious or life-threatening manifestations primarily affect*** individuals aged from birth to 18 years...
- **If program qualifies for the designation, Sponsor can request PRV at time of Dossier submission – however, must be the first indication for the NME**
- **Ongoing debate: program impact? Right program?**

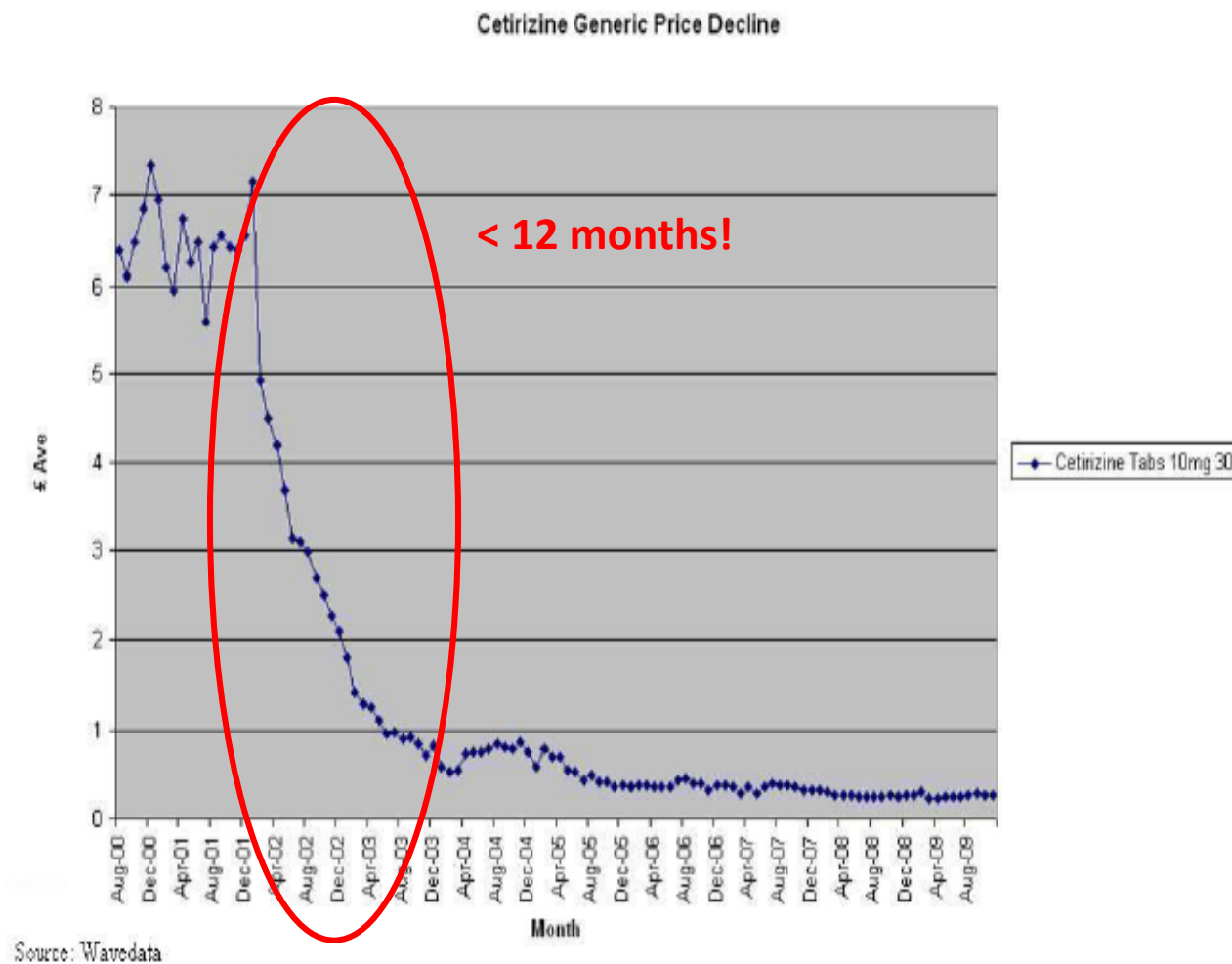


Defining Value: The ‘Denominator’

- Essentially, the *detractors from value*
- Cost
 - Rises asymmetrically from early through late phase development
 - ‘Failing fast’ allows for more efficient utilization / redeployment of resources
 - Resources (money and people) are limited – even in large multi-national companies – while each program thesis must ‘stand on it’s own’, *program investments are assessed comparatively across portfolio*
- Time
 - Time value of money (\$1 today vs. \$1 ten years from now)
 - Intellectual property / exclusivity time horizon – where is the Rx in life cycle?
- Risk – in my perspective, *the most impactful value detractor* (but can be mitigated!)
 - Feasibility – efficient patient access
 - Translatability
 - Dx understanding (clearly understood natural history vs. multi-phenotype)
 - Pharmacology understanding (and tie to above)
 - Regulatory path (and harmonization / or lack thereof)

Where is the Rx in it's Life Cycle?

- Example of typical small molecule value erosion – Cetirizine
- Typical small molecule pattern: 5 years of growth, 5 years of 'maintenance'; exposure/decline
- 80+ % of value will be lost in < 12 months following end of exclusivity
- Not a strong (financial) rationale for subsequent R&D investment – capital likely to be better deployed toward new innovation
- Biologics (mABs, RNAi, cell-based Tx, etc.) erosion not as severe, but inevitable



Defining Value: The ‘Denominator’

- Essentially, the *detractors from value*
- Cost
 - Rises asymmetrically from early through late phase development
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 - Resources (money and people) are limited – even in large multi-national companies – while each program thesis must ‘stand on it’s own’, *program investments are assessed comparatively*
- Time
 - Time value of money (\$ today vs. \$ 10 years from now)
 - Intellectual property / exclusivity time horizon – where is Rx in life cycle
- Risk – from my perspective, *the most impactful value detractor* – risk is *multiplicative*
 - Feasibility – efficient patient access
 - Translatability
 - Dx understanding (clearly understood, singular Dx natural history vs. multi-phenotype Dx)
 - Pharmacology understanding (and tie to above)
 - Regulatory path (and harmonization / lack thereof)

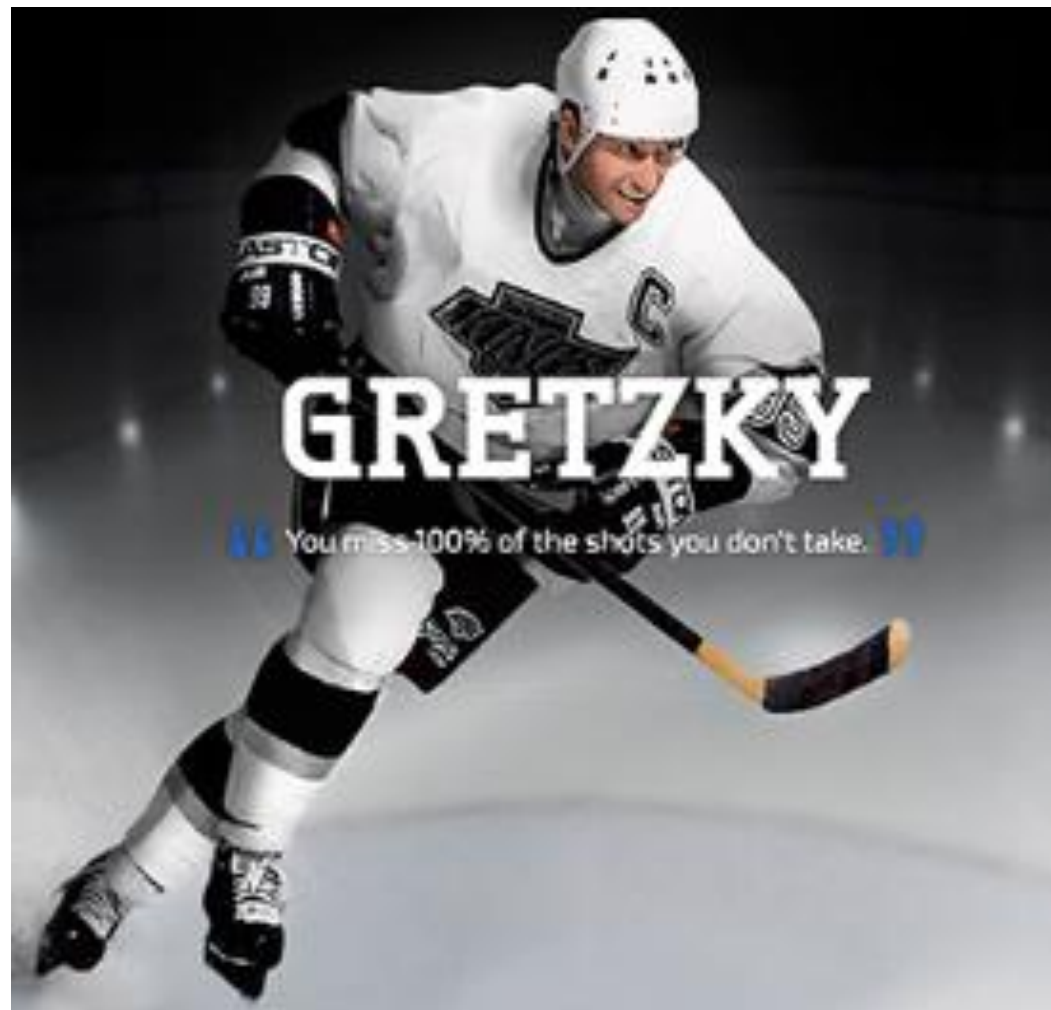
Practical Dimensions of Risk

- **Probability of *Technical Risk***
 - Study trial / center feasibility (will the trial complete in forecasted time – *time value of money*) – other trials competing for patients or failed with Rx in same class previously?
 - Predictive non-clin / translational models – can we replicate human Dx?
 - Do we understand Dx natural history and precisely how Rx should intercept Dx?

- **Probability of *Regulatory Risk***
 - Blazing a new trail vs. established pathway
 - Are global regulatory agencies harmonized?

- **Probability of *Commercial Risk***
 - Impact to prescribing information for primary indication/application?
 - ‘Strategic alignment’?
 - Can/does our field-based team have access to prescribers for new application to assure safe / appropriate use?
 - “It’s not about where the puck is...it’s about where the puck is going to be.” The Great One
 - Opportunity cost

- **Can we / how do we mitigate identifiable risks?**



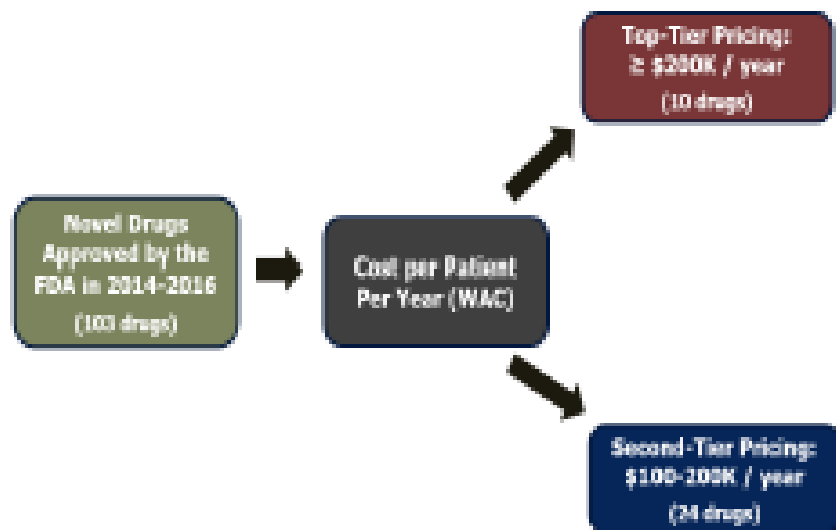
Other Considerations: Can trial design impact *the denominator*?

- Can we consider avoidance of pro-active recruitment of control group?
 - Bayesian analysis referencing a published, representative control group?
 - Have any Dx natural history studies been completed?
 - RWE / RWD as control?
- Can we considered non-traditional trial designs?
 - Have you considered a validated biomarker (or validating a biomarker) as a study endpoint? Becoming more and more accepted of an approach...
 - ‘Basket trial’ design – intervention in homogenous disease phenotype arms vs. all-comers?
 - May highlight patient subgroups where Rx may have more impact and potentially enrich subsequent trial design

Other Considerations: Nothing is as easy as it seems!

- For the most part, every collaborator company will have / need:
 - Quality control and assurance oversight
 - Certainty regarding cGXP compliance
 - Center training regarding appropriate storage/use/disposal of the investigational medication
 - Assurance of within-center staffing adequacy
- The more of these topics above are buttoned up at an investigational site, the *less impact to the denominator* for the company

Other Considerations: Payers



Many of them address patients with Rare Diseases

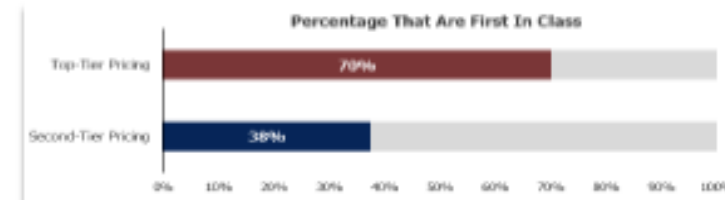
Drugs for Rare Diseases account for:

45% (46) of all 103 novel drugs approved by the FDA between 2014-2016

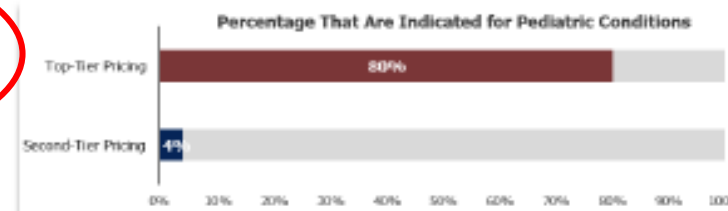
91% (31) of 34 drugs priced ≥ \$100K

100% (10) of 10 drugs priced ≥ \$200K (Top-Tier Pricing)

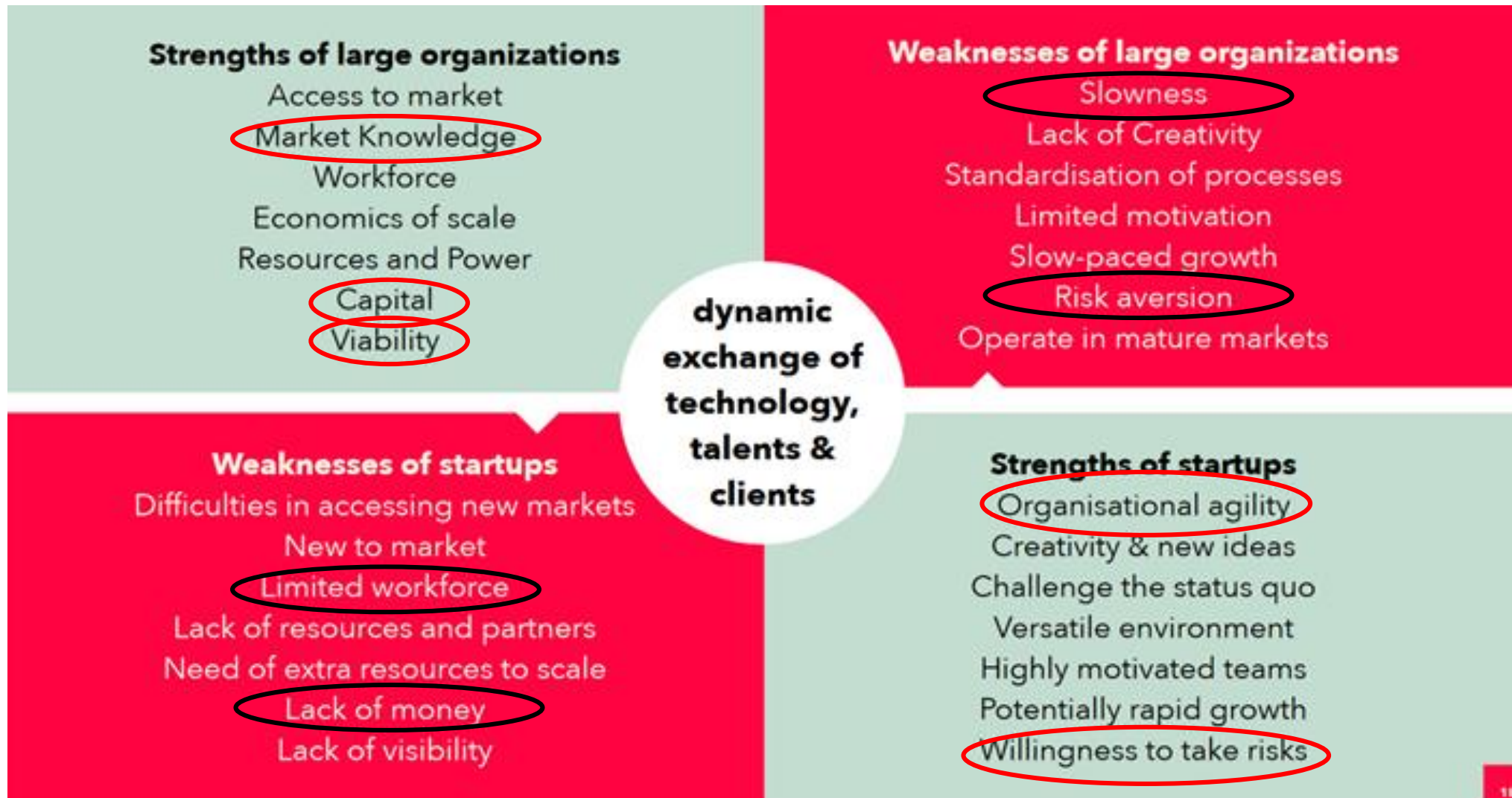
Innovation matters: **First-In-Class** status gives you pricing leverage as well as access to **Fast-Track Designation** and other development mechanisms



The Top-Tier list is dominated by drugs for Pediatrics



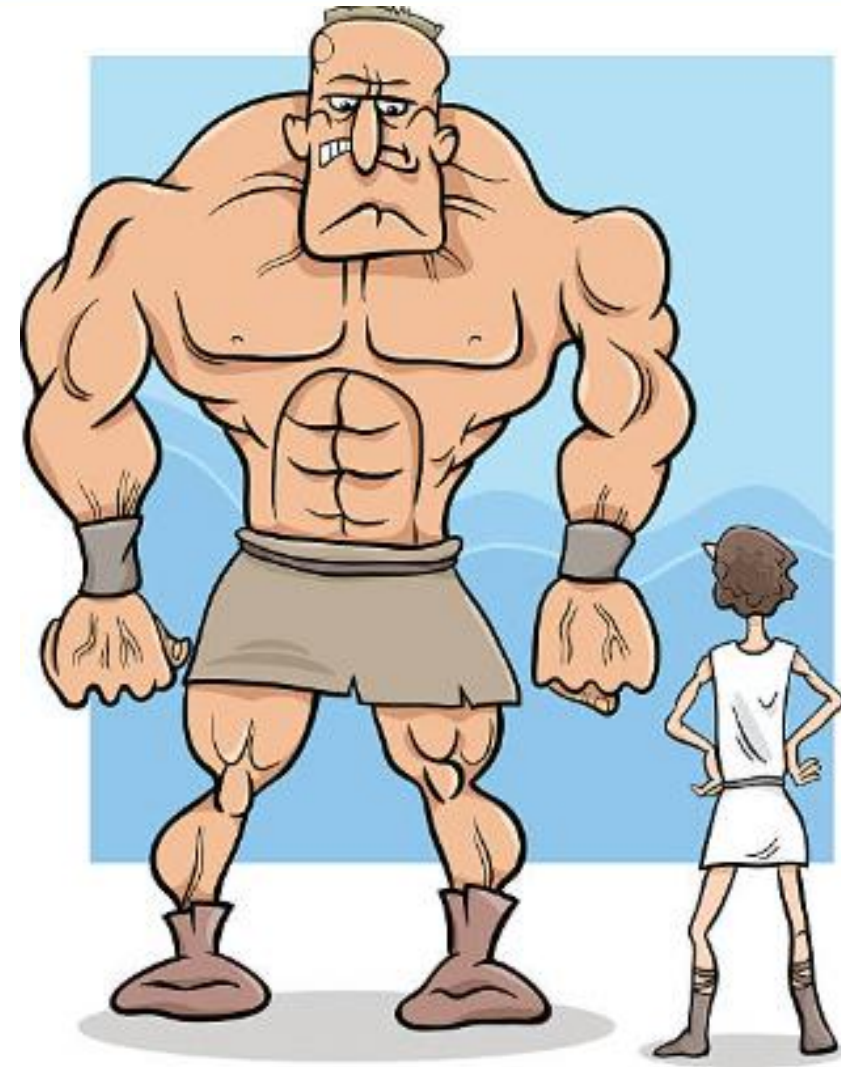
Large vs. Small Co's: What I've Learned



Large vs. Small Co's: A Few Things to Think About

- Large Co's:
 - Increasingly open to external innovation
 - Most have portal-based systems to 'pitch' your idea
 - Many have internal VC groups – completely different assessment and often times, a different approach toward collaboration
 - Don't expect things to move quickly (unless an outright *no*)

- Small Co's:
 - Love to hear about new applications for their technology
 - May be severely cash-constrained – may only have cash to next milestone (and only *earn the right* to secure further capital if the most recent milestone was positive) = *no fungible capital*
 - Would you consider a 'Rx-only' collaboration and bear all other study costs via your institution / other funding source (eg. SBIR)?
 - Where is the next company milestone in relation to your project? Is there a risk that the company may not remain solvent through your project time horizon?





- PIPs
- PSPs
- Waiver



- Peds-Centric Indications from approved product portfolio
- WRs



- Eye towards early portfolio
- Strategic 'Peds-First'?

Implications for Pediatric / Neonatology Development Investment

- Best case to pique interest:
 - Project aligns with business unit / company strategy
 - Representative, reproducible translational model identified
 - Homogeneity in selected patient population (or defined phenotype)
 - Clear understanding of Dx target natural history and how proposed pharmacology will effectively intercept Dx (*ideally data driven*)
 - Validated biomarker – LT follow up is always acceptable if not on critical path for registration
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- Second base case to pique interest:
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- Neonatologist clinical investigators and their study teams could be the best resource to help industry insiders ‘handicap’ the *denominator*

For Example...

	ARDS	ROP	BPD	NEC
Well established translational model	-	+++	+/-	+/-
Likely evidence of target engagement in early PoC study	+++	+++	++	?
Target engagement predictive of clinical outcome	-	+++	-	?
Primary clinical outcome < 1 year CA	+++	+++	?	?
Homogeneous patient population	-	+	-	-
Harmonized regulatory pathway through full development	++	++	++	++
Strategic Alignment for Co	-	+++	+	+

For Example...

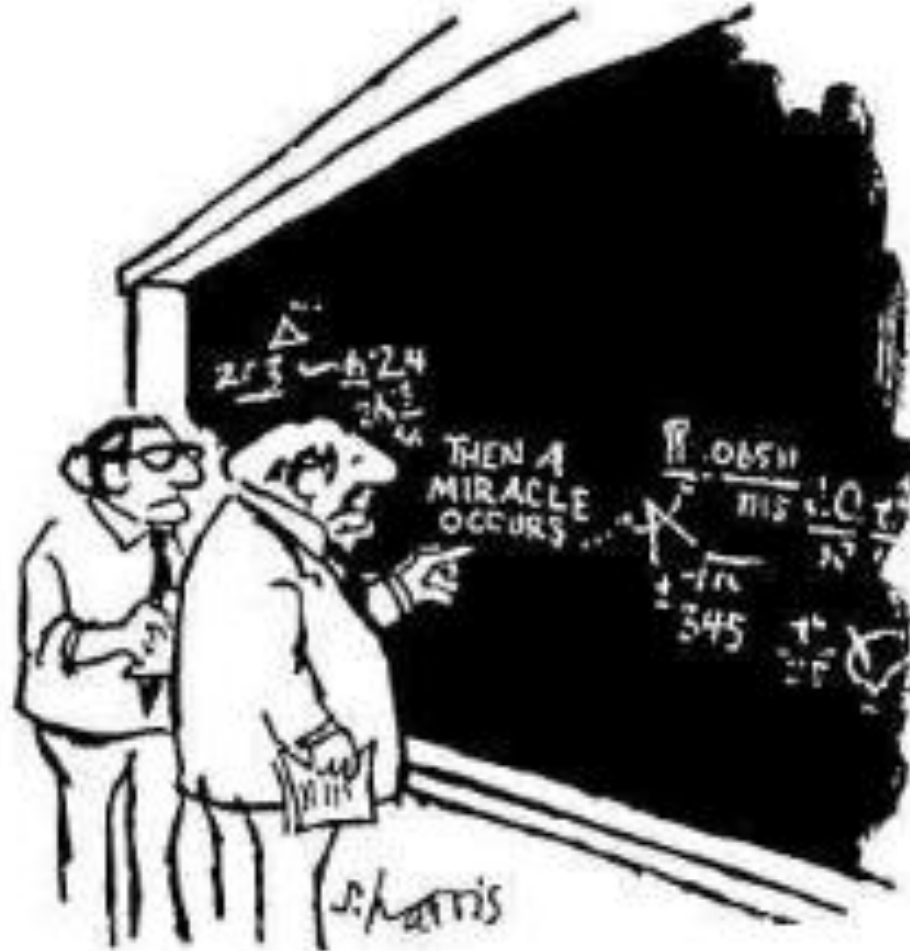
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Primary clinical outcome < 1 year CA	+++	+++	?	?
Homogeneous patient population	-	+	-	-
Harmonized regulatory pathway through full development	++	++	++	++
Strategic Alignment for Co	-	+++	+	+

Closing Thoughts

- Think win/win for all involved parties:
 - Remember the *numerator & denominator*
 - Teach us how to *reduce risk*
- Rare disease focus is a *new normal* for Life Science Co's – large and small
 - ~ 50% of all ongoing Rx development programs
 - 75+ % of rare Dx begins in childhood
 - It appears that payers will support rare pediatric Tx's
- Curative Tx's are within reach
 - Several co's interested in well-understood, mono-genetic disorders
- We want to work with you
- *Please don't tell anyone about the industry secrets I shared with you today!*



Thank You!



"I THINK YOU SHOULD BE MORE EXPLICIT
HERE IN STEP TWO."



International Neonatal Consortium

Session III: Addressing Neonatal Needs within the Current Environment

Ed Connor (I-ACT for Children), Chair



1:00 p.m. – 1:05 p.m. Welcome - Joseph Scheeren, President and CEO, Critical Path Institute

1:05 - 1:15 p.m. INC at Four Years: Neonatal Growth and Predicted Long-Term Outcomes

SUSAN McCUNE, DIRECTOR, OFFICE OF PEDIATRIC THERAPEUTICS, FDA

1:15 p.m. – 2:30 p.m. *Educating the Neonatology Community on the Drug Development Process*, RON PORTMAN

Session I: Setting the Scene, Gerri Baer (OC/FDA), Chair

- Panel: Robert Ward (U-Utah), Susan McCune (OC/FDA), Laura Fabbri (Chiesi)

2:30 p.m. – 3:00 p.m. Coffee Break

3:00 p.m. – 4:25p.m.

Session II: Harnessing the Science, Christina Bucci-Rechtweg (Novartis), Chair

- PANEL: NORMAN BARTON (Takeda), CHRIS MILNE (Tufts CSDD), THOMAS MILLER (BAYER)

4:25 p.m. – 5:30 p.m.

Session III: Addressing Neonatal Needs within the Current Environment, Ed Connor (I-ACT for Children), CHAIR

- **PANEL: SUSAN McCUNE (OC/FDA), AGNES KLEIN (HEALTH CANADA), APRILE PILON (Trove Therapeutics), MARY SHORT (Lilly), MARK TURNER (U-Liverpool), JENNIFER DEGL (Speaking for Moms and Babies, Inc), ANNE ZAJICEK (NIH/OD), KELLE MOLEY (MARCH OF DIMES), JAMES BAUMBERGER (AAP)**

Questions/Discussion:

- 1. What does each panelist see as the single most important obstacle to advancing innovative drug development for neonates? That is, why has there been so little progress measured by approved products?*
 - Culture
 - Leadership and advocacy
 - Focus/prioritization
 - Scientific “readiness”
 - Clinical trials “readiness”
 - Funding, commercialization, incentives, sustainability
 - Other
- 2. What are the most important opportunities for moving the field forward and changing the current situation?*
- 3. What can INC do to address the challenges and what is need from others?*



International Neonatal Consortium

Education Session – Educating the Neonatology Community on the Drug Development Process

Closing Thoughts

Christina Bucci-Rechtweg – co-Chair



“Becky. Joy. Zoe.”

Degl J, Discenza D, Sorrels K. Remembering the Power of Stories in Pediatric Research. J Peds. 207: 14-17. 2019.
[https://www.jpeds.com/article/S0022-3476\(18\)31718-9/pdf](https://www.jpeds.com/article/S0022-3476(18)31718-9/pdf)

Jennifer Degl’s pre-read. Session III.




Neonatal Mortality: Global Health Crisis

- ❖ Global toll:
 - Neonatal period accounts for 40% of all deaths of children under 5 (over 3M in 2010)
 - Average daily mortality during neonatal period is 30x higher than post-natal period
 - Of 15M pre-term births in 2010, 1M died (WHO 2012 Update on Neonatal Conditions)
- ❖ Global death ranks for Neonatal Encephalopathy and Neonatal Sepsis decline from 17th and 20th in 1990 to 24th and 25th, respectively, in 2010 (Global Burden of Disease Study 2010, Rafael Lozano et al, The Lancet Dec 15/22/29 2012; 380: 2095 et seq)
- ❖ US has 66% more neonatal deaths than comparable OECD country average; even recent 13% decrease in US mortality rate was eclipsed by 23% decrease in comparator countries (Kamal & Gonzales, Infant Mortality in US, Kaiser family Foundation in 2015)
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“Very enlightening. I’m a mother and grandmother but knew none of this. I would have guessed neonatal care by now would be an inexact science *at minimum*. *Now I don’t know who to feel pity for more; the babies or the medical staff.*”

- Sharon Roark

Megan Scudellari. Giving newborns medicine is a dangerous guessing game. Can we make it safer? STAT. Jan 2017.

A decorative horizontal bar at the bottom of the slide, consisting of four colored segments: grey, blue, light blue, and yellow.

Accelerating the development of safe and effective therapies for neonates.

The consortium will address the need for measurement and assessment of clinical outcomes in neonates through teams that share data, knowledge, and expertise to advance medical innovation and regulatory science.

May 19, 2015

- Best case to pique interest:
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International Neonatal Consortium

THANK YOU

