American Course on Drug Development and Regulatory Sciences

Pediatric Drug Development Workshop

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University of California, San Francisco
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Department of Bioengineering
and Therapeutic Sciences

The Role of Regulatory Policy on the Pediatric Therapies of Tomorrow

Presentation Developed By…

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Disclosures, Affiliations, and Acknowledgements

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Disclosures

The views and opinions expressed in the following PowerPoint slides are those of Christina Bucci-Rechtweg and should not be attributed to Novartis Pharmaceuticals, or any organization with which the presenter is employed or affiliated.

Looking Back

Historical Triggers

Tragedies affecting children lead to regulatory policy change


U. S. Races Death to Save 700 From Elixir

Recovery of Fint Bottles Sold to Patients Goal as Deaths From Poison Reach 36

Diptheria antitoxin (1901) — labeling

- (1902) Biologics Control Act*
- Set standards and required licensure for pharmaceutical firms making vaccines

Elixir Sulfanilamide (1937) — safety

- (1938) Food, Drug & Cosmetic Act
- Required that drugs be labeled with adequate directions for safe use; Mandated pre-market approval of the FDA for all new drugs

Thalidomide (1961) — efficacy

- (1962) Kefauver-Harris Drug Amendments Act
- Required manufacturers to prove medicines are both safe and effective for consumption

*1906 – Pure Food and Drugs Act

1977 AAP Committee on Drugs Policy statement

May 1972

"It is not only ethical but also imperative that new drugs to be used in children, be studied in children ... So the benefits of therapeutic advances will become available to all who may need them."

Global Policies Shaping Pediatric Drug Development

Pediatric Policy Initiatives

Slide Courtesy: C-Path Institute's
Global Pediatric Clinical Trials Network

Key initiatives

AAP Cmte on Drugs Policy statement

US FDAMA "carrot"

ICH E11 Guidelines

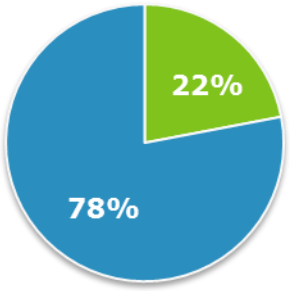
US BPCA Renews "carrot"

EU Pediatric Regulation "carrot & stick"

US FDAAA Renews "carrot & stick"

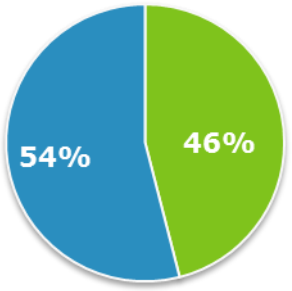
US FDASIA "carrot & stick" permanent; Peds PRV; FDA Neonatal expertise

1970 1980 1990 2000 2010



Yes
No

Proportion of medicines in Physician's Desk Reference with information relating to children



Yes
No

Pediatric Research Policies

Global view

US, EU, Switzerland^	• Formal legislation mandating pediatric research within an evolving environment • US: PREA (obligation), BPCA (incentive), FDASIA • EU: Pediatric Regulation • Switzerland: Therapeutic Products Law (obligation and incentive)
Japan*, Canada*	• Encourages voluntary pediatric data submission with incentives
Australia, New Zealand, Taiwan	• Encourages voluntary pediatric data submission with **no** incentives
China, Turkey, Russia, Asia Region, Latam Region, Middle East & Africa	• No pediatric policy

Non-government policy setting entities: APEC, WHO, IFPMA, ICH

* Actively considering policy changes which may include obligations; ^ Law passed in Mar 2016 (expected implementation 2018)

PREA = Pediatric Research Equity Act; BPCA = Best Pharmaceuticals for Children Act; FDASIA = FDA Safety & Innovation Act; APEC = Asia-Pacific Economic Cooperation; WHO = World Health Organization; IFPMA = International Federation of Pharmaceutical Manufacturers & Associations

Pediatric Legislation (1/2)

United States

1997

- **FDA Modernization Act (FDAMA)**
- Created pediatric exclusivity *incentives* with voluntary submission of data via a FDA Written Request (WR)
- May be outside of scope of adult indication

1998

- **Pediatric Rule**
- FDA requires *mandatory* pediatric development within the adult indication

2002

- **Best Pharmaceuticals for Children Act (BPCA)**
- *Reauthorized pediatric exclusivity**
- Provides process for off-patent pediatric drug development
- Public posting of results & reporting of AEs for 1 yr after exclusivity

2003

- **Pediatric Research Equity Act (PREA)**
- *Mandatory* pediatric development; Creates pediatric Advisory Cmte
- Applies to: (1) All pediatric age groups; (2) Same indication as in adults; (3) Drugs & biologics

* 6 mos extension attached to all active patents and other exclusivities at the time of the granting; Biologics Price Competition and Innovations Act (BPCIA) in 2009 extended pediatric exclusivity to biologics by granting 6 mos of protection to all active exclusivities – NOT to patents

Pediatric Legislation (2/2)

United States

2007

- **FDA Amendments Act (FDAAA)**
- Reauthorizes PREA (Title IV) & BPCA (Title V)

Require reauthorization on a 5-year cycle → "sunset"

2012

- **FDA Safety & Innovation Act (FDASIA)**
- **Permanently reauthorizes** BPCA & PREA (Title V)
- **Pediatric Rare Disease Priority Review Voucher** program
- Enhance FDA neonatal expertise; WRs lacking neonatal-specific assessments must include rationale

Pediatric Legislation

European Union

2007

EU Pediatric Regulation

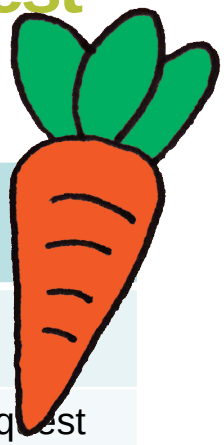
- Obligation to generate data in compliance with a Pediatric Investigational Plan (PIP)*
- Compliance with and completion of the PIP determines reward: (1) 6 mos extension of the SPC, or (2) 2 yrs extension of the market exclusivity for orphan drugs
- May be outside of scope of adult indication

* Pediatric data must be generated in compliance with a PIP as part of a marketing authorisation application or line extension unless a decision on Waiver or Deferral has been granted

Link to Regulation (EC) 1901/2006:
http://ec.europa.eu/health/files/eudralex/vol-1/reg_2006_1901/reg_2006_1901_en.pdf

Facilitating the Inclusion of Pediatric Considerations into Adult Development

US: Pediatric Research Equity Act (PREA) and Best Pharmaceuticals for Children Act (BPCA)



	US PREA	US BPCA
Pediatric development	**Mandatory**	**Optional**
Name of the pediatric plan	Paediatric Study Plan (PSP)	Proposed Pediatric Study Request (PPSR); Written Request (WR)
Timing	No later than 60 days after EoP2 meeting	Any time
Reward	No reward	6-mos patent extension + exclusivity*
Biologics	Included	Included
Orphan	Exempted	Included
Scope of pediatric development	Adult indication	Not limited to adult indication (mechanism of action based)
Labelling	Studies must be labeled	Studies must be labeled

*Biologics exclusivity only

When do you need a Pediatric Study Plan (PSP) under PREA?

New medicinal products (drug or biologic) not already marketed in the US

Products already marketed:
New indications, new pharmaceutical forms and new routes of administration

Except for 505(j) products/ANDA generics

Products already marketed: New strength

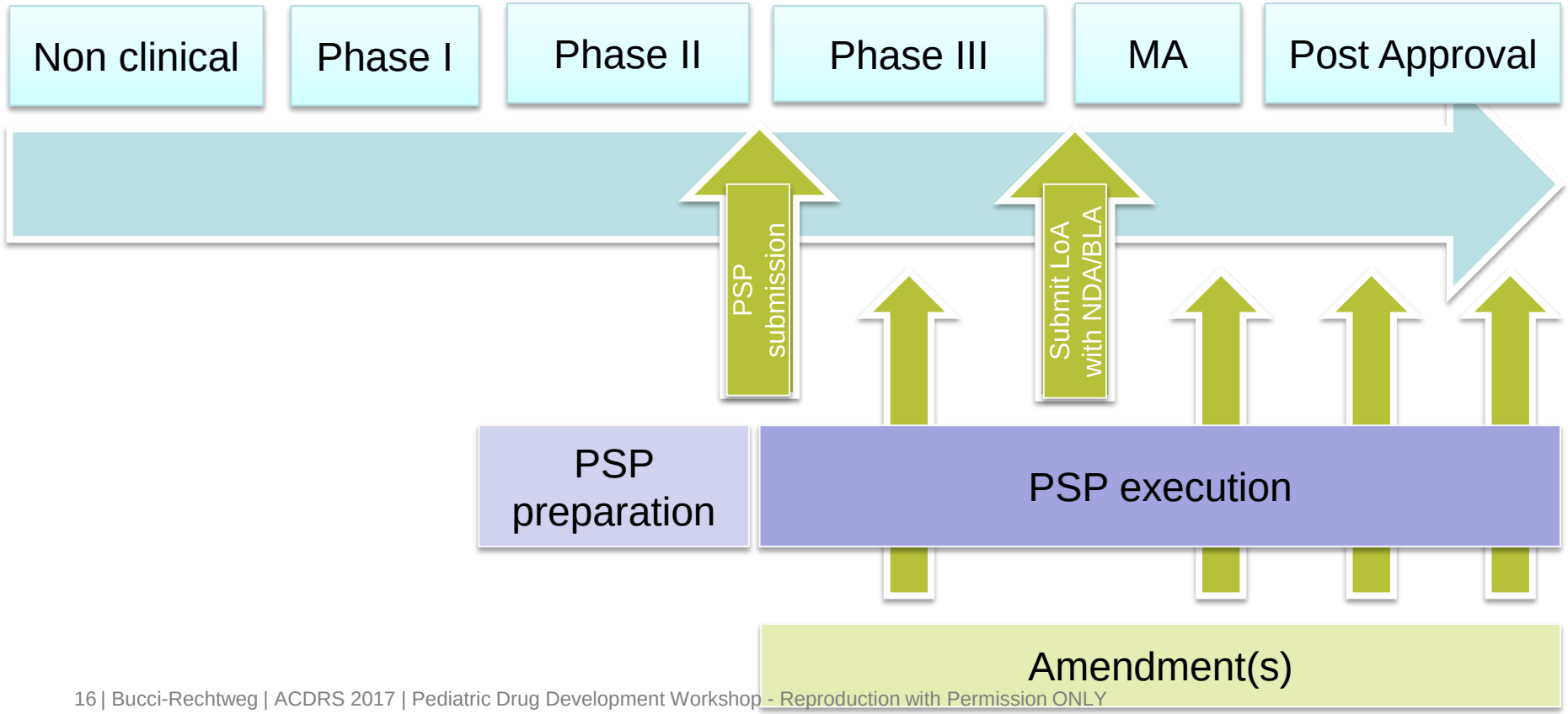
Unless related to a new indication/ form/ route of administration

Product granted an orphan designation

Optional PPSR (WR)

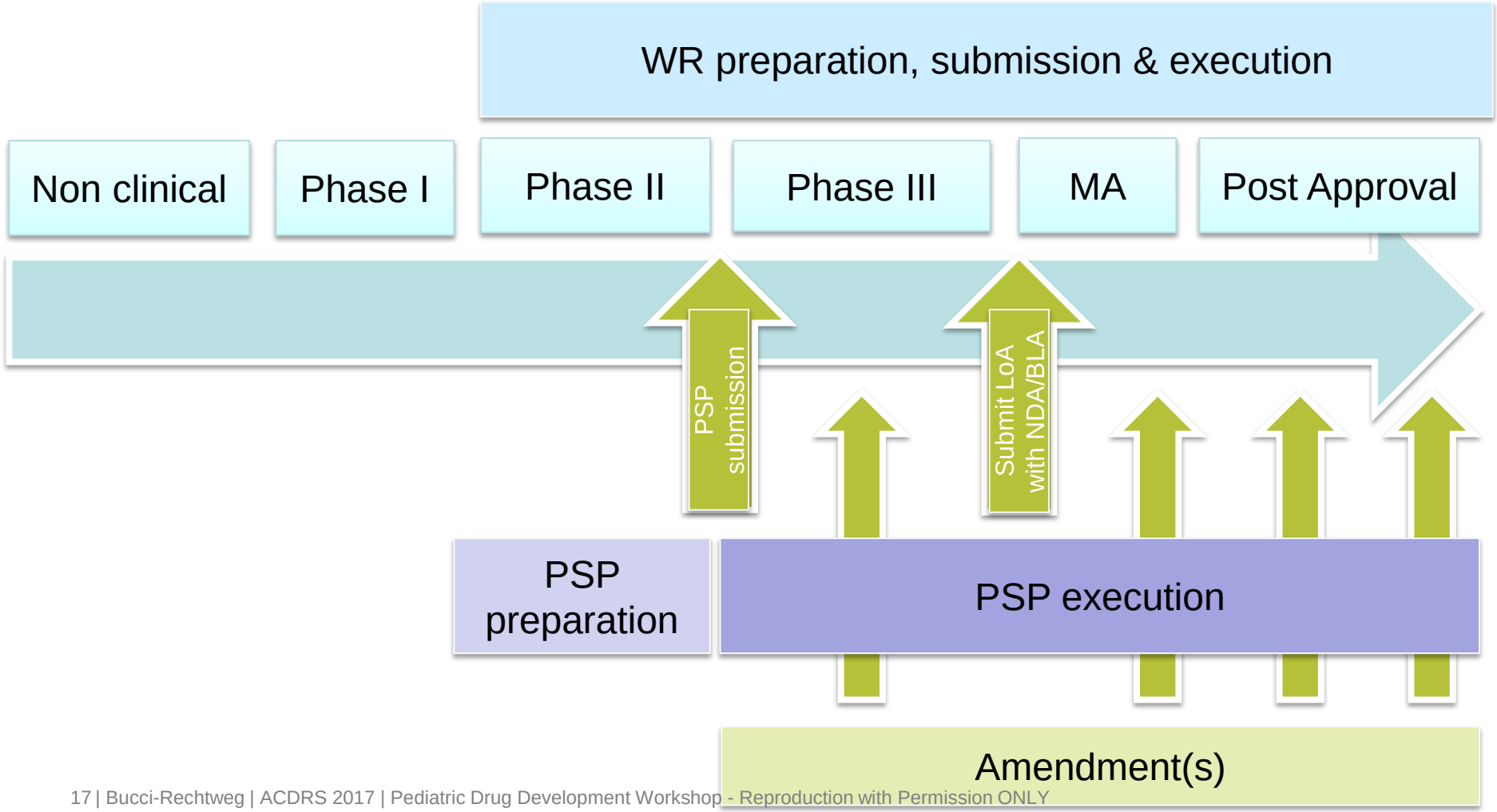
When do you submit a Pediatric Study Plan (PSP) under PREA?

- Submit to the IND no later than 60 days after the EoP2 meeting
- In the absence of an EoP2 meeting, submit as early as practicable, but no later than the start of confirmatory program



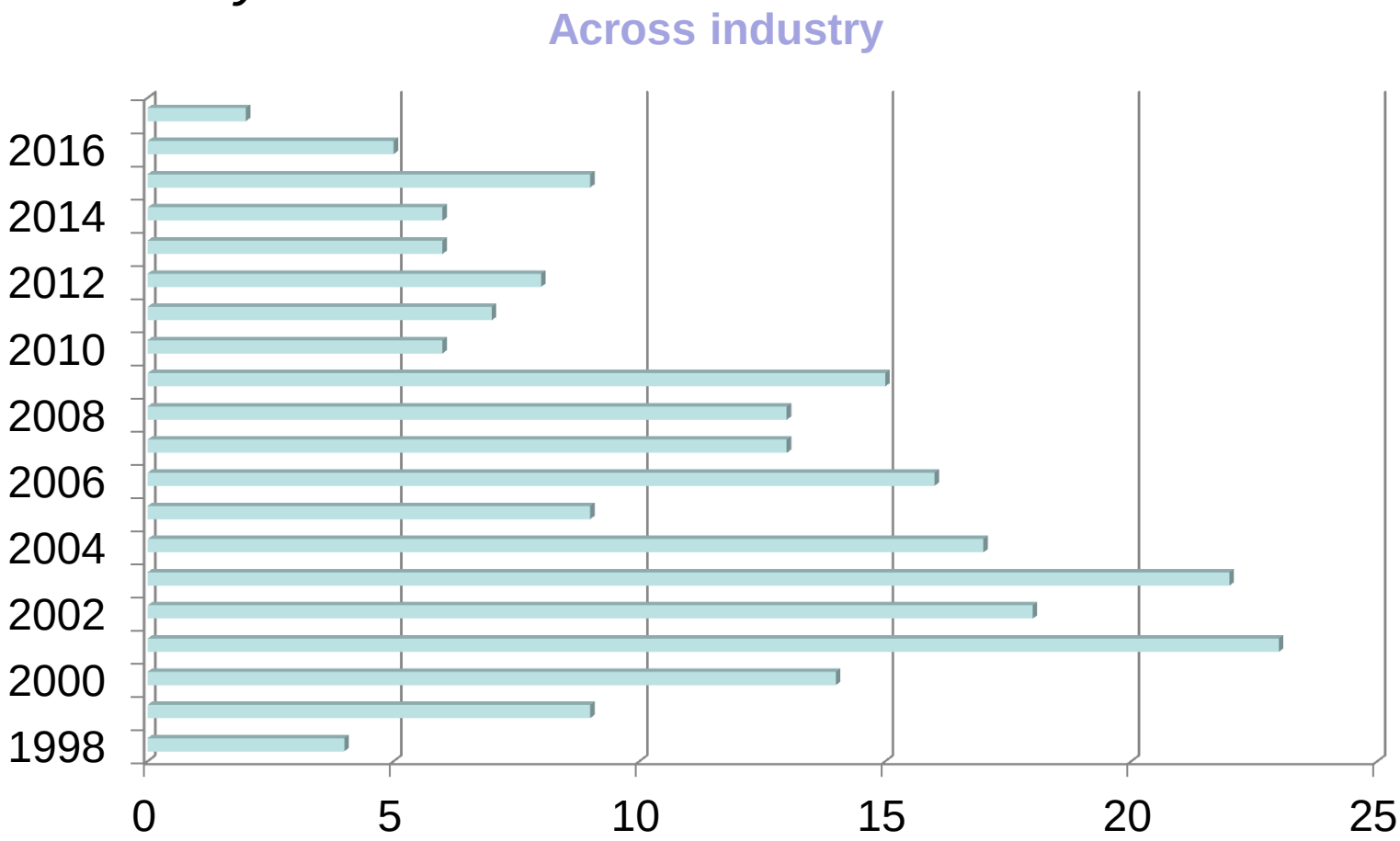
When do you submit a Proposed Pediatric Study Request (PPSR) under BPCA?

- FDA will not issue a WR for studies previously submitted to the agency



Rewards granted under BPCA

222 Completed Written Requests have led to pediatric exclusivity



Source: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM223058.pdf (accessed 06 Mar 2017)

EU: When Do We Need a Paediatric Investigation Plan (PIP)?

New medicinal products not already authorized in the EU — YES

Products already authorized :
new indications, new pharmaceutical forms and new routes of administration — YES

if the active substance is protected by a SPC

Products already authorized (with a patent): new strength — NO

unless related to a new indication/ form/ route of administration

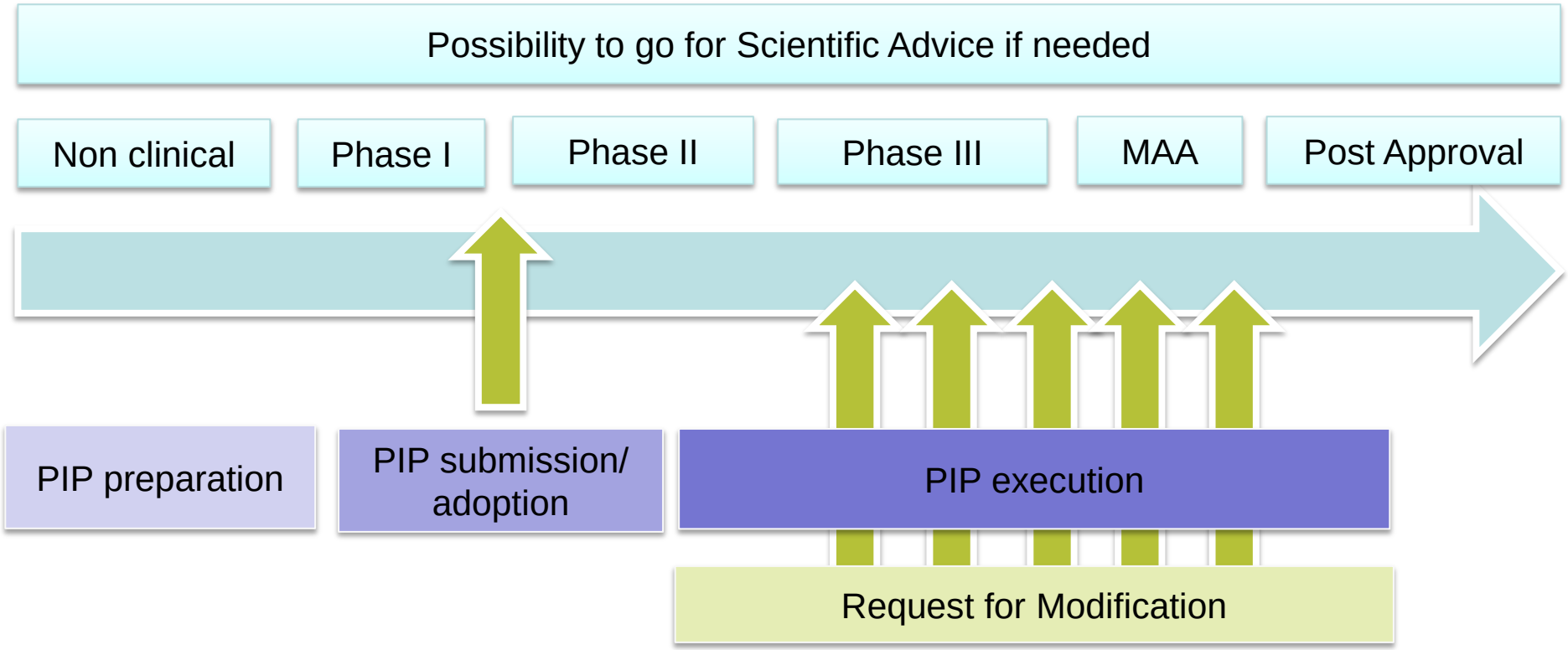
Old Products/ Off patent — NO

optional PIP (PUMA)

PIP requirement applies for Orphan medicinal products: Orphan → Separate PIP/ Separate MA
Separate development (i.e. indications not submitted at the same time) → Separate PIPs

When do we submit a PIP?

PIP submission early during product development



Ensure early dialogue between the sponsor and the PDCO (early interaction pilot)
Ensure that pediatric development becomes an integral part of adult development program
In time for studies to be conducted in the pediatric population before MAAs are submitted if appropriate

Facilitating Pediatric Innovation*

* Regulatory policy facilitating the regulatory review of innovative medicines (including pediatric medicines) that address unmet medical need in the treatment of serious or life-threatening conditions

Facilitating Innovation:

Selected Expedited Programs from key ICH Regions

Key characteristics of the 3 most recent expedited programs*

	United States	European Union	Japan
Scheme	Breakthrough Therapy Designation (BTD)	PRIME scheme	Sakigake Designation
Target product	• Drugs • Biologics	• Medicines for human use • Advanced-therapy medicinal products (ATMPs) such as genes, cells or tissue engineering.	• Medicines • Medical devices • regenerative medicines
Qualifying criteria	• A medicine that is intended to treat a serious condition • Preliminary clinical evidence indicates may demonstrate substantial improvement over available therapies on a clinically significant end point or end points	• A medicine that may a major therapeutic advantage over existing treatments, or benefits without treatment options • A medicine has to show its potential to benefit patients with unmet medical needs based on early clinical data • Academic sector and small-sized companies can apply earlier than the above development stage.	• Innovativeness of the product • Treatment for which the earliest commercialization is required for target diseases • Highly effective treatment against the target medical condition • Develop the product rapidly and file an application for approval in Japan, ahead of other countries/simultaneously
Regulatory Features	• All Fast Track designation features • Intensive guidance on an efficient drug development program, beginning as early as phase 1 • Organizational commitment involving FDA senior managers • Option for priority review	• Enable accelerated assessment • EMA dedicated contact point who will coordinate the support offered throughout the scheme • Better use of existing regulatory and procedural tools as scientific advice at key development mile stone etc.	• All Priority Review designation features • Prioritized clinical trial and pre-application consultation • Assigned PMDA manager as a concierge • Post-marketing safety measures • Advantage to price

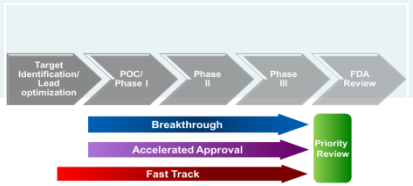
*Key differences highlighted

UCSF

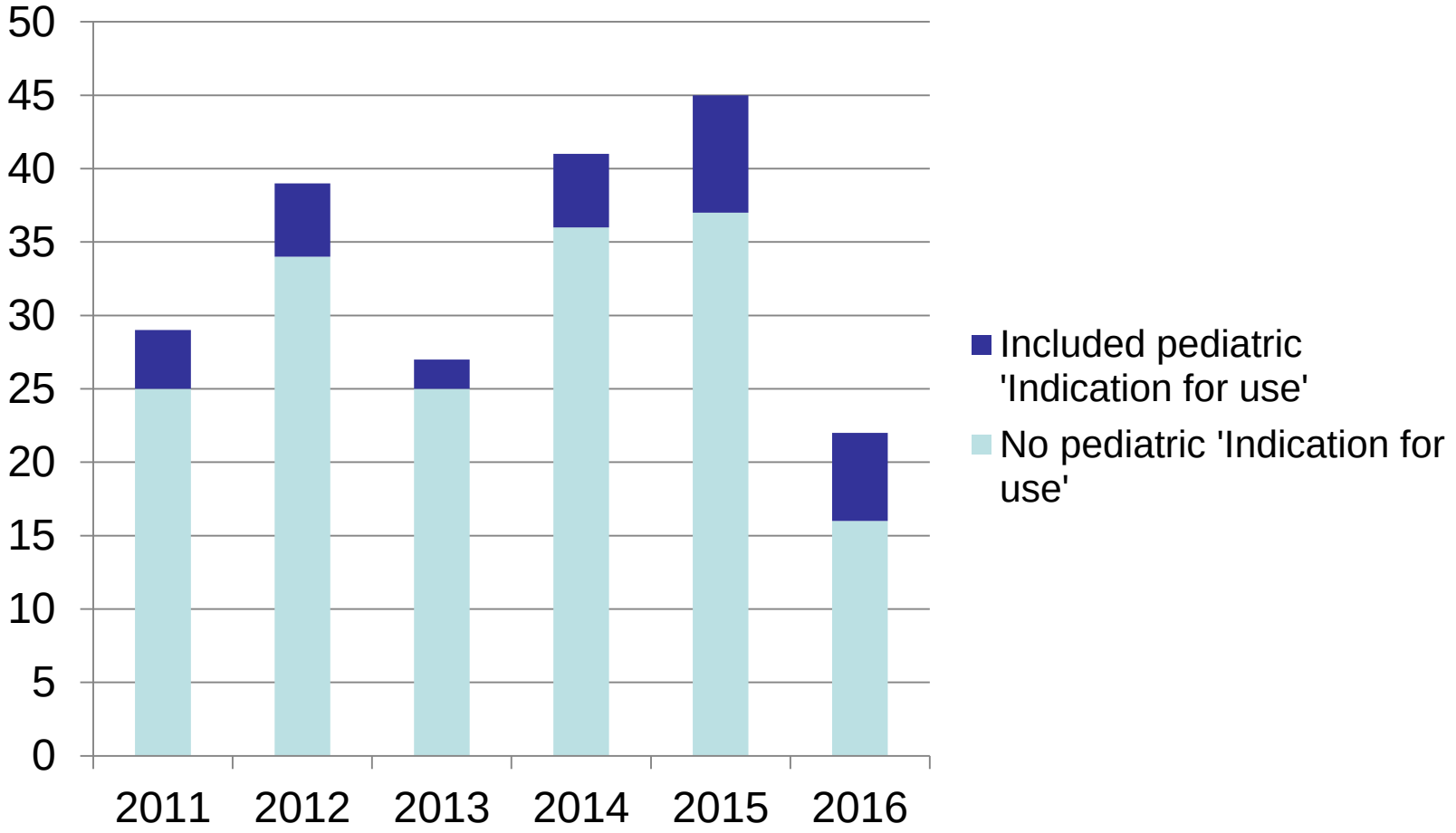
US Expedited Development Mechanisms

Goal: To facilitate and expedite the development and review of innovative medicines that address unmet medical need in the treatment of serious or life-threatening conditions

	Accelerated Approval	Fast-Track Designation	Priority Review	Breakthrough Therapy Designation
Eligibility	1. Treat serious or life-threatening diseases 2. Provide meaningful therapeutic benefit over existing therapies 3. Surrogate endpoint reasonably likely to predict clinical benefit	1. Intent to treat broad range of serious or life-threatening diseases 2. Potential to fill an unmet medical need	Offer major advances in treatment over existing therapies	1. Treat serious or life-threatening diseases 2. Early clinical evidence of substantial improvement over existing therapies
Designation	No formal process	Can be requested by sponsor at any time	Requested by sponsor at time of NDA/BLA submission	Can be requested by sponsor at any time after IND submission
FDA Review-Response	N/A	60 days	45 days	60 days
Clinical Development	Conditional approval granted using surrogate endpoint from phase II trials or interim phase III data; controlled trials with hard clinical endpoints required to confirm clinical benefit	Earlier and more frequent communication	N/A	Abbreviated or condensed development; earlier and more frequent communication; delegation of senior reviewers and cross-disciplinary review team
Review Process	NDA/BLA data submitted in one package; standard 10-month review	Option for Rolling NDA/BLA submission Official review clock begins when last module is submitted	NDA/BLA data submitted in one package; review time shortened to 6 months	NDA/BLA data submitted as they are accumulated; review time shortened



By the numbers:
U.S. FDA Novel Drug Approvals
(2011 – 2016)

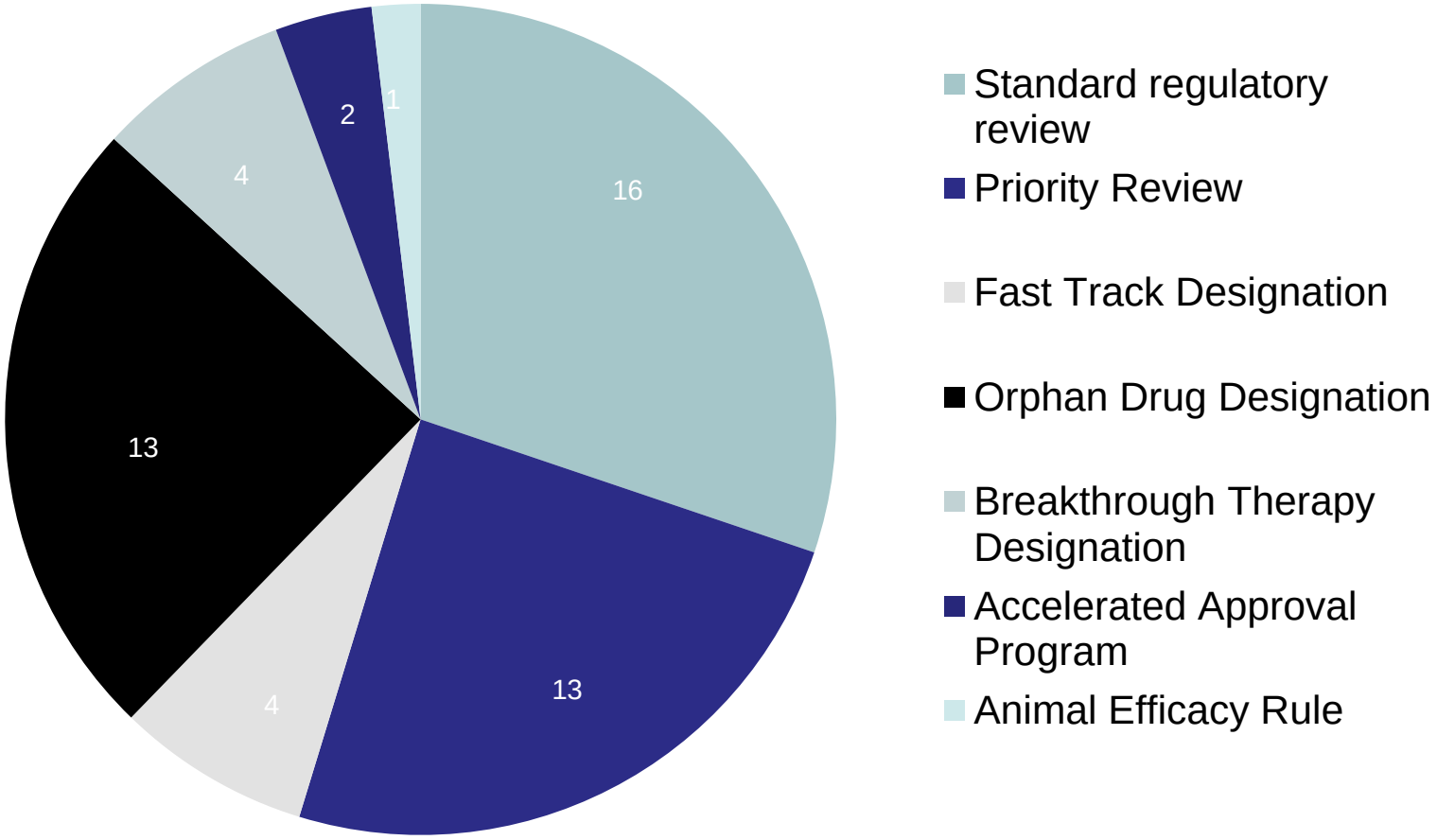


Source: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/default.htm

By the numbers:
U.S. FDA Pediatric Novel Drug Approvals

Regulatory Mechanisms Utilized

2011 – 2016
(30 products)



Source: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/default.htm

Facilitating Innovation: Development Incentives

Orphan Drug Designation

- The Orphan Drug Act (ODA) grants special status ("orphan designation" [OD]) to a drug or biological product to treat a rare disease or condition upon request of a sponsor
  - Criterion specified in the ODA and FDA's implementing regulations (21 CFR Part 316)
- OD qualifies the sponsor of the drug for development incentives, including
  - ✓ Orphan products grants program
  - ✓ Tax credits for qualified clinical testing
  - ✓ Waiver of drug user fee for the marketing application (MA)*
  - ✓ Orphan drug exclusivity
- Common EMA/FDA template

*Unless it includes an indication for another condition for which the drug was orphan designated

https://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/HowtoapplyforOrphanProductDesignation/ucm124795.htm

Facilitating Innovation: Development Incentives

Pediatric Rare Disease Priority Review Voucher (PRV)

- Created under FDA Safety and Innovations Act (FDASIA) to encourage development of drugs and biologics for “rare pediatric diseases (RPD)”
- ➢ If a sponsor receives approval of a “RPD product application”, the sponsor is eligible to receive a PRV which can be redeemed, or transferred to another sponsor, to obtain priority review of another application ineligible for priority review
- Rare Pediatric Disease (*definition*)
  - ✓ Is a serious or life-threatening disease in which the serious or life-threatening manifestations primarily affect individuals aged from birth to 18 yrs AND
  - ✓ Is a rare disease or condition (includes diseases /conditions that affect fewer than 200,000 in the US)

By the numbers:
U.S. FDA Pediatric Novel Drug Approvals

Rewards for innovation

30 novel pediatric products (2011 - 2016)

- ✓ 7 Pediatric Rare Diseases Priority Review Vouchers
  - 1 in 2014
  - 4 in 2015
  - 2 in 2016
- ✓ 1 Tropical diseases Priority Review Voucher (pediatric)

Source: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/default.htm

Shaping our Future

May 2007

“We are made wise not by the recollection of our past,

but by the responsibility of our future.”

- George Bernard Shaw

Pediatric drug development today

Fundamental change of culture

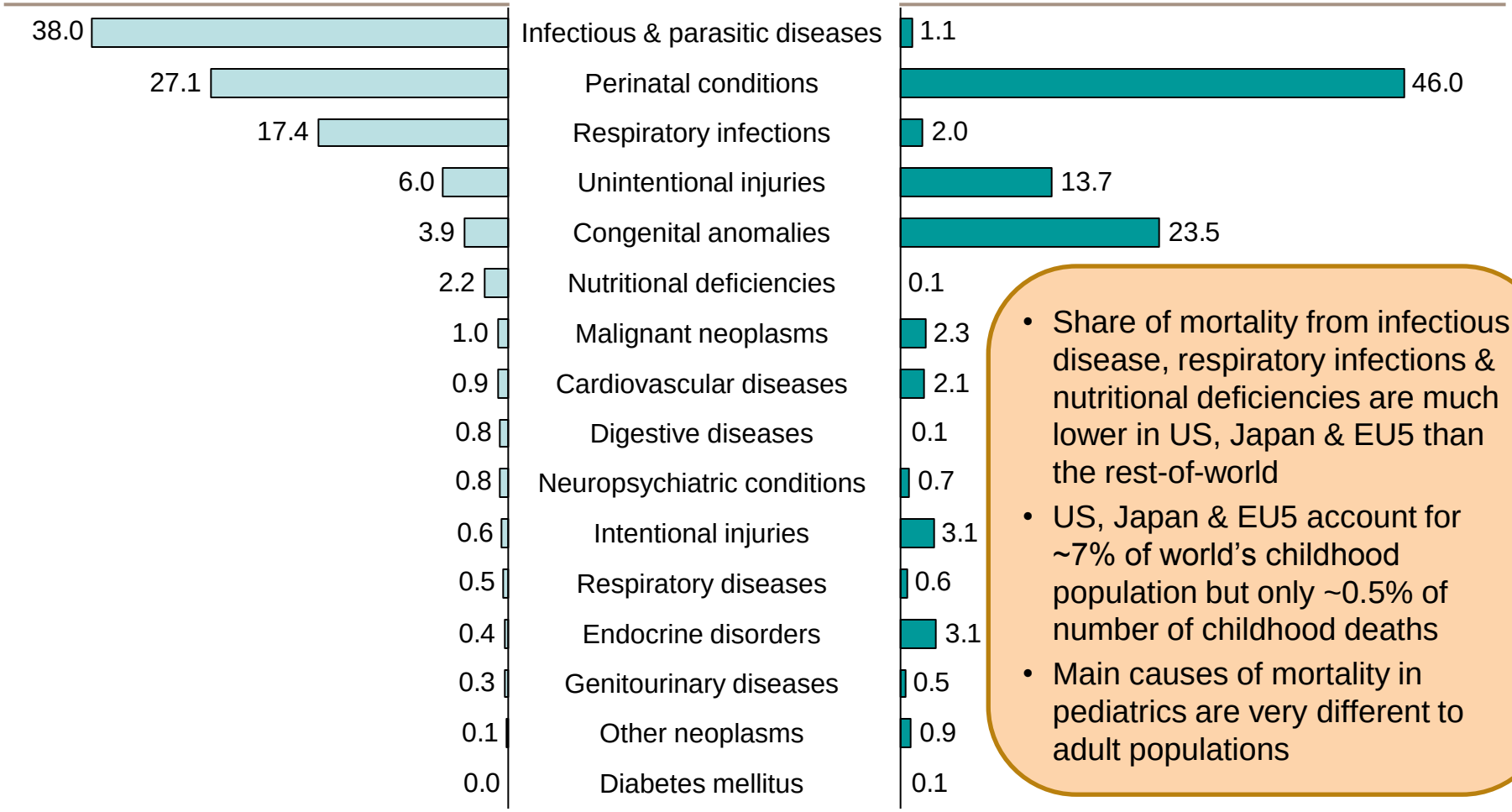
Pediatric program development an integral part of product development

Pediatric innovation from bench to bedside

However ...

Significant differences exist in numbers & causes of pediatric death in established markets vs rest-of-world

Causes of death in 0-14 yr olds, 2008, %



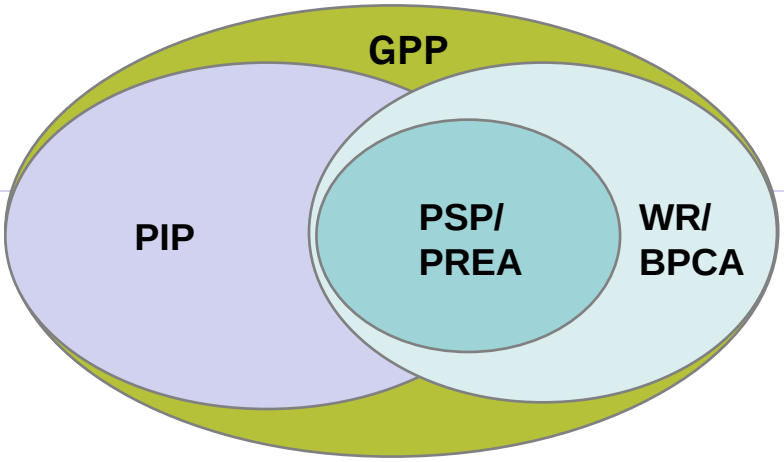
- Share of mortality from infectious disease, respiratory infections & nutritional deficiencies are much lower in US, Japan & EU5 than the rest-of-world
- US, Japan & EU5 account for ~7% of world's childhood population but only ~0.5% of number of childhood deaths
- Main causes of mortality in pediatrics are very different to adult populations

Source: WHO Department of Health Statistics and Informatics

Objective: Toward a Better Global Alignment

Building a Global Pediatric Development Strategy

- ✓ Global pediatric program (GPP) – In early stage development, consider all potential pediatric uses of the mechanism of action both independent of and within adult indication(s) across the global markets
- ✓ PIP – Assessment, deferral or waiver for on-label indication and the broader condition
- ✓ PSP/PREA – Assessment, deferral or waiver for on-label indication
- ✓ WR/BPCA – Voluntary pediatric research for pediatric reward



Toward a Better Future

- Off-label use of pediatric therapeutics remains commonplace
  - Outside of specialty pediatrics where tremendous unmet medical need exists, less urgency in general pediatric domain to support 'industry research' → advance the conversation (public-private partnerships, other)

- Small sample sizes lead to challenging study recruitment and highly competitive research environments
  - Need for: Smarter study design; Innovation in technical research and development, pharmacometric approaches, and pediatric-focused global regulatory pathways

- Much of pediatric drug development remains dependent upon adult development
  - Current regulations do not fully address the need
  - RoI for pediatric drug development remains unchanged and existing incentive structures are not necessarily addressing significant unmet need → policy innovation, incentives, sub-population specific policy (i.e. neonates)

- Current pediatric regulatory pathways introduce significant administrative burden (on industry, agency, and research community at large)
  - Need for shared global research objectives prioritizing unmet need
  - Simplify regulatory process and continue movement towards global harmonization

Thank You

Contact: Christina Bucci-Rechtweg

Christina.buccirechtweg@novartis.com

Other valuable slides for reference only

US: Incentives & Reward under BPCA

Pediatric burden to address a public health need, compensated by financial reward

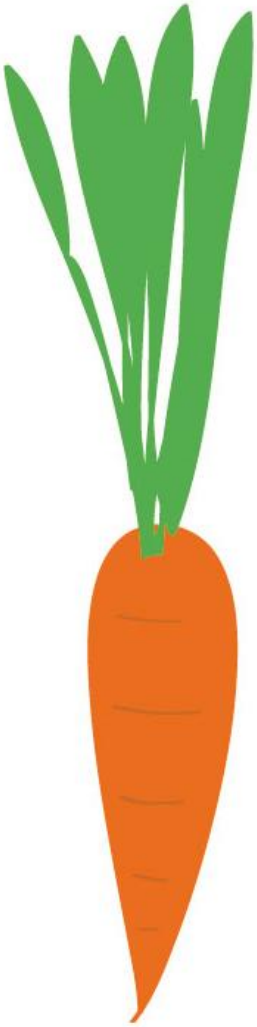
Medicinal Product	Reward
Drug products	6 months pediatric exclusivity attached to all existing patents and added to 5 (NME) and 3 (non-NME) years of data exclusivity
Orphan Products	6 months of pediatric exclusivity added to 7 years of orphan exclusivity
Biological Products	6 months of pediatric exclusivity added to 12 years of data exclusivity

- Applications and assessment of PPSR: free of charge
- Exclusivity is granted when studies are complete and meet the conditions of the WR
  - Efficacy need not be demonstrated, however, the studies must provide “useful” information

EU: Incentives and Reward under Paediatric Regulation

Paediatric burden compensated by financial reward

Medicinal Product	Reward
New Medicinal product	6 months SPC extension
Orphan Medicine	2 additional years of market exclusivity In addition to 10 years market exclusivity
Off patent Medicine (PUMA – optional/voluntary)	8+2 years of data & market protection (but only on paediatric data)



For a medicinal product with multiple orphan indications in different conditions:

- Reward granted for each entirely separate orphan designated indication for which a PIP has been completed and complied with

US: What is a PREA Waiver or Deferral?

Waiver

- FDA may grant a Full or Partial Waiver; Disease-specific Waiver
- Studies are impossible or highly impractical
- The product would be ineffective or unsafe in pediatric patients
- No meaningful therapeutic benefit over existing therapies; Unlikely to be used by a substantial number of pediatric patients
- An age appropriate formulation can not be developed

Deferral

- Product is already approved for use in adults
- Additional safety and efficacy data are needed prior to start of pediatric studies
- Other reason(s) as agreed with the agency

Requires strong scientific & technical rationale

EU: What is a PIP Waiver?

Need strong scientific & technical justifications or grounds related to public health

Waiver

Product specific waiver

Class waiver: Product developed for conditions not affecting children (Parkison, Alzheimer)
List of conditions exempt from the requirement of a PIP
Class waiver under review by EMA (Missed opportunities for children)

Full or Partial waiver: A waiver of the pediatric development can be granted for all (full waiver) or subsets (partial waiver) of the pediatric population

Grounds for waiver : PDCO waives development in children for lack of efficacy, lack of safety, lack of significant therapeutic benefit or when disease does not occur in children

If **waiver revoked** : 36 months to allow time for PIP to be agreed/paediatric studies to be initiated before MAA submission

Pediatric development mandatory in the EU for new medicines unless a product-specific or a class waiver is granted

EU: What is a PIP Deferral?

Need strong scientific & technical justifications or grounds related to public health

Deferrals

A deferral allows postponing the initiation and/or the completion of the measures in the PIP
In order not to delay the MA in adults
and to perform studies in children when it is safe to do so.

Full or Partial deferral = All or some of the measures are deferred
(often until after the studies in adults have been conducted)

Full deferral = Deferral of all measures set in the EMA decision /
No studies have to be completed at the time of submission

Grounds for deferral: safety or ethical issues / avoid delaying MA in adults

If deferral on a PIP, obligation to submit to the EMA **Annual Reports** to
provide an update on progress with pediatric studies
(once a year, starting when MA is granted until PIP is final)

Even when studies are deferred,
PIP include details & timelines of the paediatric studies