How the RACE for Children Act Impacts Pediatric Oncology Drug Development:

Understanding Current Regulations and Enhancing your Global Strategy

March 17, 2020
Pediatric Oncology
Treatment Perspectives

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Covance Clinical Development Services
Pediatric Cancer Overview

Cancer is a leading cause of death in children

Most common diagnoses are leukemias, brain and CNS tumors, soft tissue sarcomas, neuroblastoma, and kidney tumors

Adolescents - brain/CNS tumors, lymphomas, leukemias, gonadal germ cell tumors, thyroid cancer, melanoma
Distribution of Pediatric Cancer Types

- Leukemia: 25%
- CNS: 26%
- Neuroblastoma: 4%
- Non-Hodgkin Lymphoma: 5%
- Wilms Tumor: 6%
- Rhabdomyosarcoma: 2%
- Thyroid Carcinoma: 6%
- Bone Tumors: 5%
- Germ Cell Tumors: 6%
- Retinoblastoma: 2%
- Melanoma: 2%
- Other: 5%

Adapted from: [www.curesearch.org/Number-of-Diagnoses](http://www.curesearch.org/Number-of-Diagnoses), with reference to American Cancer Society, Cancer Facts and Figures (2018), and National Cancer Institute (2017)
Epidemiology of Adult vs. Pediatric Cancers

<table>
<thead>
<tr>
<th></th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>All cancers</td>
<td>100</td>
<td>1,762,450</td>
<td>67.1%</td>
</tr>
<tr>
<td>Breast</td>
<td>15</td>
<td>268,600</td>
<td>89.9%</td>
</tr>
<tr>
<td>Lung and bronchus</td>
<td>13</td>
<td>228,150</td>
<td>19.4%</td>
</tr>
<tr>
<td>Prostate</td>
<td>9</td>
<td>174,650</td>
<td>98.0%</td>
</tr>
<tr>
<td>Colon and rectum</td>
<td>8</td>
<td>145,600</td>
<td>64.4%</td>
</tr>
<tr>
<td>All pediatric cancers</td>
<td>&lt;1</td>
<td>11,050 (2020)</td>
<td>*84.0% (2020)</td>
</tr>
</tbody>
</table>

* Of the pediatric “non-survivors” life expectancy is still 70+ years

5-Year Survival Rate, Age 0–19

Source: Surveillance, Epidemiology, and End Results (SEER) Program (seer.cancer.gov)
SEER 9 areas based on follow up of patients into 2015

https://curesearch.org/5-Year-Survival-Rate Surveillance, Epidemiology, and End Results (SEER) Program (seer.cancer.gov)
Average Years of Life Lost to Cancer (2016)

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Average Life Lost (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Childhood (Ages 0-19)</td>
<td>68.3</td>
</tr>
<tr>
<td>Breast</td>
<td>18.8</td>
</tr>
<tr>
<td>Melanoma</td>
<td>16.5</td>
</tr>
<tr>
<td>Lung and Bronchus</td>
<td>15</td>
</tr>
<tr>
<td>Colon and Rectum</td>
<td>15.7</td>
</tr>
<tr>
<td>Prostate</td>
<td>10</td>
</tr>
</tbody>
</table>

Average Age of Death for Pediatric Cancer Patient (age 0-19): 10.4 years

Source: Surveillance, Epidemiology, and End Results (SEER) Program (seer.cancer.gov)
Historical Perspective of Treatment

- Prior to 1940s, childhood cancer was essentially not treatable
- Sidney Farber at Boston Children’s Hospital – advent of “chemotherapy” for children
- Further advances at the National Institutes of Cancer
- Advent of cooperative groups to develop treatments for pediatric cancers

Credit: Dana-Farber Cancer Institute
Historical Perspective of Treatment

**Mid-1970s**

5-year survival rate for new diagnosis was 58% for children (0-14 years), and 68% for adolescents (15-19 years).

**2008-2014**

5-year survival rate for children – 83.4%

adolescents – 84.6%

**Leukemia**

5-year survival rate ages 0-14 years went from 57% in 1975 to 92% in 2012

However, prognosis in other diseases have not changed (DIPG, metastatic sarcoma)
Principles of Treatment for Pediatric Cancers

Surgery  
Chemotherapy  
Radiation  
Biologic/novel therapy

Focus on *cure* with intensive therapy regimens

- Not the case for some adult protocols
- Young adults may have better outcomes on pediatric vs adult protocols
60% of children who survive cancer suffer long-term side effects.
Survival and Resulting Challenges

► With improvement in treatments, more children can become adults who survived childhood cancer

► What does survival mean?
  • Toxicity from therapy – acute and late effects
  • Secondary cancers – leading cause of non-relapse death (~20% at 30 years after diagnosis)
  • Neurocognitive deficits from cranial radiation, some chemotherapy
  • Infertility/sexual dysfunction
  • Psychosocial stressors
  • Early mortality of cancer survivors

► Importance of survivorship clinics
FDA Approvals for Pediatric Oncology

Many chemotherapies approved for use from 1950s-1970s are still in use (Mercaptopurine for ALL – 1953)

**Pediatric-specific new approvals 2000-2018:**

<table>
<thead>
<tr>
<th>Year</th>
<th>Approval</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>Clofarabine</td>
<td>ALL</td>
</tr>
<tr>
<td>2004</td>
<td>Arsenic trioxide</td>
<td>APML</td>
</tr>
<tr>
<td>2005</td>
<td>Erwinia asparaginase</td>
<td>ALL</td>
</tr>
<tr>
<td>2005</td>
<td>Nelarabine</td>
<td>ALL</td>
</tr>
<tr>
<td>2007</td>
<td>6-mercaptopurine</td>
<td>liquid formulation</td>
</tr>
<tr>
<td>2011</td>
<td>Dinutuximab</td>
<td>NBL</td>
</tr>
<tr>
<td>2014</td>
<td>Tisagenlecleucel</td>
<td>ALL</td>
</tr>
<tr>
<td>2017</td>
<td>Avelumab</td>
<td>Merkel cell carcinoma</td>
</tr>
<tr>
<td>2017</td>
<td>Emapalumab</td>
<td>HLH</td>
</tr>
<tr>
<td>2018</td>
<td>Larotrectinib</td>
<td>Solid tumors with NTRK fusion</td>
</tr>
</tbody>
</table>
Challenges for Future Drug Development

Chemotherapy can only go so far
Targeted therapy in kids has some notable successes:

- Validated targets on leukemic lymphoblasts – CD19, CD22
- BCR-ABL (Philadelphia chromosome)
- Crizotinib (ALK) – anaplastic large cell lymphoma
- Vandetanib (RET) – MEN type 2B associated medullary thyroid carcinoma
Challenges for Future Drug Development

All of these depend on understanding of the driver mutation

Yet – many studies that show no efficacy in children

Why

► Pediatric molecular mutational landscape is different than that of adults
► Children are not “little adults” – tumors are fundamentally different than in adults
► Drugs that are selected for peds studies come from adults (but can take years to get to pediatric studies)
► Very few actual druggable targets in kids
  • Fusion proteins (EWS-FLI1, leukemia fusions) but these don’t generate druggable oncoproteins such as kinases, but often more elusive targets such as transcription factors
Other Considerations

► Over the past 20 years FDA has approved 48 protein kinase inhibitors – nearly all are administered orally
  • Flat dosing that works well in adults may not work for young children
  • Liquid formulations are often hard to develop; compounding is either impossible or difficult

► Difficulty of integrating targeted agents with chemotherapy – necessary in some cases, but not always the best way to determine efficacy

► Toxicity of checkpoint inhibition in children
Recent Successes

Larotrectinib (NTRK) – dramatic responses in children with fusion-positive tumors

ALK or ROS inhibitors for inflammatory myofibroblastic tumors

MEK/BRAF inhibition in low-grade gliomas

Checkpoint inhibition in high grade gliomas who have underlying germline biallelic mismatch repair deficiency
Future Directions

1. Continue to develop understanding of the underlying biology of pediatric tumors
2. Preclinical studies to identify targets
3. Judicious use of combination therapies with chemotherapy
4. Single agent approach may not be sufficient
5. Drugs that “fail” in adults may have different applications in children
Understanding Current Regulations and Enhancing Your Global Strategy

Alicia M. Baker McDowell, DRSc, MS
Executive Strategist, Head of Biosimilars Center of Excellence, Strategic Product Development Consulting
Covance
Historically, drugs have been used in children without the same level of evidence as has been obtained in adults.

Why?

- Studies in children were discouraged
- Belief that dosing could be determined by body weight (“little adults”)
- Inherent difficulties in conducting pediatric trials
- Lack of pediatric regulations/legislation to incentivize or require sponsors to conduct pediatric trials
History of Pediatric Legislation in the U.S.

- **1974** AAP Committee on Drugs issues guidelines for evaluating drugs for pediatric use
- **1977** AAP issues guidelines for ethical conduct in pediatric studies
- **1979** FDA requires sponsors to conduct pediatric clinical trials before including pediatric information in the labeling
- **1992** Agency proposed Pediatric Labeling Rule and proposes extrapolation of efficacy from other data
- **1994** Final Rule on Pediatric Labeling. Formalizes Extrapolation of Efficacy; manufacturers to update labeling if pediatric data existed; HOWEVER, it allowed a disclaimer to the labeling for drugs not evaluated in children
- **1994** Pediatric Plan to encourage voluntary development of pediatric data
- **1997** FDAMA creates pediatric exclusivity provision (voluntary), provides 6-month exclusivity incentive
- **1998** Pediatric Rule (mandatory): products are required to include pediatric assessments if the drug is likely to be used in a “substantial number of pediatric patients” (50,000) or if it may provide a “meaningful therapeutic benefit”
- **2002** Pediatric Rule declared invalid by DC Federal Court; the rule exceeded FDA’s authority
- **2002** FDAMA reauthorized as BPCA. Maintains 6-month exclusivity added to patent life of the active moiety. Creates Office of Pediatric Therapeutics (including ethicist). Mandates pediatric focused safety reviews
- **2003** PREA re-establishes many components of the FDA’s 1998 pediatric rule. Orphan products are exempted
- **2007** FDAAA Reauthorizes BPCA & PREA for 5 years: Pediatric Review Committee (PeRC) formed. Studies submitted will result in labeling. Negative and positive results of pediatric studies will be placed in labeling
- **2012** FDASIA legislation makes permanent BPCA and PREA; PAC was permanently reauthorized under section 507
- **2017** Incorporated as Title V of the FDA Reauthorization Act (FDARA), enacted August 18, 2017 (Research to Accelerate Cures and Equity (RACE) for Children Act)
- **2019** Creating Hope Reauthorization Act, priority review voucher program for sponsors developing treatment for a rare pediatric disease
## PREA and BPCA
They Work Together

### Pediatric Research Equity Act (PREA)
- Drugs and biologics
- Required studies
- Initial pediatric study plans (iPSP) are required for all PHS applications within 60 calendar days from the End of Phase 2 (EOP2) meeting
  - Applies to NCEs, new indications, new dosage forms, dosing regimens and routes of administration unless waived or deferred
- Studies may only be required for approved indications
- Products with orphan designation are exempt
- Pediatric studies must be targeted toward labeling

### Best Pharmaceuticals for Children Act (BPCA)
- Drugs and biologics
- Introduced 6-month market exclusivity extension
- Voluntary studies
- Studies apply to all indications of the molecule and may broaden indications
- Studies may be requested for products with orphan drug designation
- Pediatric studies must be targeted toward labeling
PREA and BPCA

Intended to work together to maximize information in labeling:

All Information is Deemed Critical

Not Mutually Exclusive
<table>
<thead>
<tr>
<th>Year</th>
<th>Drug Name</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1953</td>
<td>Mercaptopurine</td>
<td>ALL</td>
</tr>
<tr>
<td>1960</td>
<td>Methotrexate</td>
<td>ALL, meningeval leukemia, osteosarcoma, NHL</td>
</tr>
<tr>
<td>1965</td>
<td>Daclomycin</td>
<td>Ewing Sarcoma, sarcoma botryoides</td>
</tr>
<tr>
<td>1965</td>
<td>Vinblastine</td>
<td>Leukemia</td>
</tr>
<tr>
<td>1969</td>
<td>Procarbazine</td>
<td>HL</td>
</tr>
<tr>
<td>1968</td>
<td>Cytarabine</td>
<td>Acute non-lymphocytic leukemia</td>
</tr>
<tr>
<td>1967</td>
<td>Thioguanine</td>
<td>Acute non-lymphocytic leukemia</td>
</tr>
<tr>
<td>1959</td>
<td>Cyclophosphamide</td>
<td>Leukemia, lymphoma, NBL, rhabdomyosarcoma, NBL</td>
</tr>
<tr>
<td>1979</td>
<td>Daunorubicin</td>
<td>ALL</td>
</tr>
<tr>
<td>1979</td>
<td>L-Asparaginase</td>
<td>Leukemia</td>
</tr>
<tr>
<td>1970</td>
<td>Rasburicase</td>
<td>Management of plasma uric acid levels at risk for TLS</td>
</tr>
<tr>
<td>1980</td>
<td>Doxorubicin</td>
<td>Wilmstumor, NBL, soft tissue sarcoma, HL, other lymphomas, ALL, AML</td>
</tr>
<tr>
<td>1988</td>
<td>Arsenic trioxide</td>
<td>APLML</td>
</tr>
<tr>
<td>2000</td>
<td>Levoleucovorin</td>
<td>Rescue after HD-MTX</td>
</tr>
<tr>
<td>2005</td>
<td>Nelarabine</td>
<td>T-cell ALL</td>
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<tr>
<td>2005</td>
<td>Clofarabine</td>
<td>Refractory ALL</td>
</tr>
<tr>
<td>2007</td>
<td>Tretinoin</td>
<td>APLML</td>
</tr>
<tr>
<td>2010</td>
<td>Rubrubicase</td>
<td>ALL</td>
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<tr>
<td>2011</td>
<td>Everolimus</td>
<td>SEGA</td>
</tr>
<tr>
<td>2013</td>
<td>Pembrolizumab</td>
<td>Refractory classical cHL, MSI-H</td>
</tr>
<tr>
<td>2013</td>
<td>Pergilastatin</td>
<td>Decrease incidence of infection, increase survival in patients exposed to myelosuppressive doses of radiation</td>
</tr>
<tr>
<td>2017</td>
<td>Pembrolizumab</td>
<td>Refractory classical cHL, MSI-H</td>
</tr>
<tr>
<td>2017</td>
<td>Dasatinib</td>
<td>Ph+CML</td>
</tr>
<tr>
<td>2017</td>
<td>Imatinib</td>
<td>Ph+ALL, Ph+CML</td>
</tr>
<tr>
<td>2017</td>
<td>Nilotinib</td>
<td>Refractory/classi first-line, or second-line, BCR-ABL positive, Ph+ CML, including Ph+ chronic myeloid leukemia, in the chronic phase</td>
</tr>
<tr>
<td>2019</td>
<td>Nilotinib</td>
<td>Ph+ CML</td>
</tr>
<tr>
<td>2018</td>
<td>Pembrolizumab</td>
<td>Refractory/classi first-line, or second-line, BCR-ABL positive, Ph+ CML, including Ph+ chronic myeloid leukemia, in the chronic phase</td>
</tr>
</tbody>
</table>

*Refer to US Prescribing Information for details.

Jingjing Ye (OB, OTS, CDER, FDA), 3rd Stat4Onc Symposium April 2019
PSPs should be submitted to FDA no later than 60 days after the EOP2 meeting.

*Even if asking for a deferral or waiver, it must be submitted at this time.*

The EU requires the submission of a Pediatric Investigation Plan (PIP) after the first in human study and before Phase 2 for each potential indication.

*Deferrals and waivers may also be requested.*
Research to Accelerate Cures and Equity (RACE) for Children Act

Signed into law as part of FDARA of 2017
Purpose is to promote reach and development of new cancer treatments for children

Pediatric investigation can be required based on molecular target
Orphan designated drugs are no longer exempt

Waivers are limited
RACE for Children Act

1. Enables earlier dialogue with FDA about pediatric studies
2. Smaller study populations will require the development of innovative study designs
3. Opportunity for collaboration
4. Independent regulatory review of pediatric data
5. List created with molecular targets and includes over 200 targets
Impact on Development

- Pediatric formulation
- Consider variability between adults and children
- Leverage adult safety and efficacy data to inform on trial design
- Preclinical data considerations
- Starting dose and dose regimen
- Appropriate endpoints and biomarkers
Impact to Global Pediatric Development

Japan does not have mandatory pediatric development but it is encouraged.

Regular exchange of information between regulators.

New US regulations promote earlier pediatric considerations.

US and EU have mandatory pediatric drug development regulations.
Pediatric Oncology Clinical Trials and the RACE Act: Minding the Gap

Kathleen A. Neville, M.D., M.S., M.B.A
Sr. Director, Pediatric Drug Development
Child Health Innovation Leadership Department
Office of the Chief Medical Officer

Johnson & Johnson
Disclosures

• Employee of Johnson and Johnson
  • The opinions expressed are mine and do not represent Johnson and Johnson

• Committee on Practice, American Society of Hematology
Why Now?
Prior to 2017-- BPCA and PREA

**BPCA**
- Drugs and biologics
- Voluntary studies with incentive
- Studies relate to entire moiety and may expand indications
- Studies may be requested for orphan indications
- Pediatric studies must be intended for labeling

**PREA**
- Drugs and biologics
- Mandatory studies
- Requires studies only on indication(s) under review
- Orphan indications exempt from studies
- Pediatric studies must be intended for labeling
Pediatric Labeling Changes 1998-2019 (n=84)
Number of Studies Completed under BPCA and PREA

Number of clinical studies

- 1990-1997: 10 studies
- 1997-2007: 400 studies
- 2007-2014: 800 studies
Number of children enrolled in trials under BPCA and PREA

Estimated number of children enrolled in clinical trials

- 1990-1997
- 1997-2007
- 2007-2014
Orphan Designation

• Orphan status given to drugs and biologics which are defined as those intended for the treatment, prevention or diagnosis of a rare disease or condition, which is one that affects less than 200,000 persons in the US or meets cost recovery provisions of the act.

• The Rare Pediatric Disease Priority Review Voucher Program says that a sponsor who receives an approval for a drug or biologic for a "rare pediatric disease" may qualify for a voucher that can be redeemed to receive a priority review of a subsequent marketing application for a different product.
FDA: Indication is the Basis for Approval

• Reflects the FDA approved usage of a drug, including any limitations of use
• Indications are uses determined to be safe and effective and for which the regulatory standard of “substantial evidence of effectiveness” was met
• When developing the indication, use of descriptors/qualifiers is considered
  • Population (demographic)
  • Disease or condition
  • Circumstance/clinical setting
  • Description of effect/outcomes

DRUG-X is indicated in combination with an aromatase inhibitor as initial endocrine-based therapy for the treatment of postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer.

https://www.fda.gov/media/109300/download
# Children versus Adults

<table>
<thead>
<tr>
<th>Kids</th>
<th>Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukemia</td>
<td>Skin</td>
</tr>
<tr>
<td>Brain and CNS tumors</td>
<td>Prostate</td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td>Breast</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>Lung</td>
</tr>
<tr>
<td>Kidney tumors</td>
<td>Colorectal</td>
</tr>
<tr>
<td>Retinoblastoma</td>
<td>Leukemia</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>Kidney tumors</td>
</tr>
<tr>
<td>Primary Bone cancer</td>
<td>Carcinoma</td>
</tr>
<tr>
<td></td>
<td>Metastatic Bone Cancer</td>
</tr>
</tbody>
</table>
Waiver and Deferrals Granted under PREA 2012-2018

* CDER data

**Waivers**
RACE for Children Act

“The RACE for Children Act addresses both loopholes and now extends PREA requirements to the development of cancer drugs for children.” –Nancy Goodman

• Incorporated as Title V of the FDA Reauthorization Act (FDARA in 2017)
  • Requires evaluation of new molecularly targeted drugs and biologics “intended for the treatment of adult cancers and directed at a molecular target substantially relevant to the growth or progression of a pediatric cancer.”
  • Molecularly targeted pediatric cancer investigation: clinically meaningful study data, “using appropriate formulations, regarding dosing, safety and preliminary efficacy to inform potential pediatric labeling.” [FDARA Title V Sec 504 (a)(3)(A) or FD&C Act Sec. 505B (a)(3)(A)].

Elimination of orphan exemption for pediatric studies for cancer drugs directed at relevant molecular targets.

https://cancerletter.com/articles/20170908_2/
Molecular Target Definition

“...A molecule in human cells that is intrinsically associated with a particular disease process, such as etiology, progression, or drug resistance. To be referred to as a target, there must be evidence that by engaging the target, either with a targeted small molecule, biologic product, or other treatment intervention, a desired therapeutic effect is produced that results in the alteration of the disease process. In other words, a molecule would not be referred to as a molecular target if there is no evidence to inform the hypothesis that its modulation (i.e., inhibition or activation) alters the disease.”

(From: FDA Briefing Document Relevant Molecular Targets in Pediatric Cancers: Applicability to Pediatric Therapeutic Investigations Required Under FDARA 2017)
The “List”

• 205 Targets
• [https://www.fda.gov/media/120332/download](https://www.fda.gov/media/120332/download)
• Only exceptions (as of 5/2019)
  • Target Symbol: AR, ESR1, ESR2, GnRHR, PSA/PSCA/PSMA
• List is all inclusive and evolving—a lot of targets have only limited data

Bottom Line—Requirement of pediatric studies is now the rule, not the exception unless proven otherwise
For all oncology products, it is now critical to conduct early assessments that inform or refute studies in children with cancer
Relevant Tumors

• Conditions that don’t have good response +/- available therapies:
  • Sarcoma & Renal
  • Rhabdomyosarcoma, Ewing sarcoma, Renal tumor
  • Neuroblastoma
  • Osteosarcoma
  • Leukemia/Lymphoma
    – B cell lineage, T cell lineage, (relapse), AML
  • Brain tumors
    – Medulloblastoma, Ependymoma, High grade gliomas
The Creating Hope Act: The Rare Pediatric Disease Priority Review Voucher (PRV) Incentive Program

• Creating Hope Permanent Reauthorization Act of 2019
  • Creates incentive for companies to develop drugs for pediatric rare diseases: a pediatric priority review voucher.
  • Entitles a company to faster FDA review of any other future drug, including non-pediatric rare disease drugs when the voucher is exercised.
  • Seeks permanent reauthorization of the Creating Hope Act (passed in 2012 and was reauthorized several times).

• The pediatric priority review voucher program has been considered to be successful:
  • Vouchers are trading at $100 million to $350 million, creating a significant incentive for pediatric rare disease drug development.
  • $2 billion in vouchers have traded, with no cost to taxpayers or patients.
  • Since the enactment of the Creating Hope Act, 19 new drugs for children with life threatening illnesses have been approved, including 2 for childhood cancers.
  • The voucher incentive is funded by the pharmaceutical industry as companies that earn vouchers by developing pediatric rare disease drugs sell vouchers to other companies.
IMPLICATIONS FOR PEDIATRIC DRUG DEVELOPMENT
IMPLICATIONS FOR PEDIATRIC DRUG DEVELOPMENT
Timing for Pediatric Drug Development & Regulatory Interactions

US

- Preclinical testing
- Phase 1
- Phase 2
- Phase 3
- EOP?
- Adult PK
- No later than
- PIP modifications
- Approved PIP required for MAA submission

EU

- PIP process begins
- No later than
- PIP modifications
- Approved PIP required for MAA submission

Written Request issued (BPCA)

210 days prior

Agreed PREA requirements

Submission & Review

Marketing Approval

PMR

Post Marketing Requirements
<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Required?</td>
<td>Voluntary</td>
<td>Required</td>
<td>Required</td>
</tr>
<tr>
<td>Scope</td>
<td>Drugs &amp; Biologics</td>
<td>Drugs &amp; Biologics</td>
<td>Drugs &amp; Biologics</td>
</tr>
<tr>
<td>Indication</td>
<td>Approved or unapproved indications</td>
<td>Approved indication only except in cancer where MoA may determine indication.</td>
<td>Approved indication is starting point. Related condition based on MoA may determine indication.</td>
</tr>
<tr>
<td>Deferrals</td>
<td>NA</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Orphan Exemptions</td>
<td>NA</td>
<td>Eliminated in 2018</td>
<td>NA</td>
</tr>
<tr>
<td>Waivers</td>
<td>NA</td>
<td>Yes. Some automatic, some negotiated.</td>
<td>Yes. Some automatic; product specific.</td>
</tr>
<tr>
<td>Exclusivity</td>
<td>6 months, moiety</td>
<td>NA</td>
<td>6 months (moiety) or 2 years (applies to orphan pediatric indication)</td>
</tr>
</tbody>
</table>

Context: Pediatric Legislation in the US and EU
EMA: Condition vs. Indication

Conditions to be studied under a PIP are based on (1) Adult Indication (2) Mechanism of Action

- Adult Indication: “only the starting point for PDCO, which can go on looking at the potential use for children”
- PIP Condition: “represent a ceiling, limiting the scope of the PDCO’s evaluation of the potential paediatric use”
- A PIP Condition must be chosen from “an independent hierarchical classification of diseases/conditions – e.g. MedDRA, WHO etc."

Information Gathering:

- Literature search
- Clinicaltrials.gov
- Discourse with FDA

Example – Choice of Condition in MedDRA
Extrapolation as Seen by EU

Extrapolation may be applied in many other areas:
- Between population subsets
- Between disease subtypes or stages, different diseases, symptoms
- Between medicines, within and between classes
- From animal studies to humans

Rationale
- Similarity of disease
- Similarity of drug disposition and effect
- Similarity of applicability of clinical endpoints
Pediatric Legislation: U.S. and EU Harmonization

• Both the US and EU have incentive and requirement programs for the development of therapeutics in pediatrics

• There are similarities and differences between the U.S. and EU pediatric legislations
  • U.S. has 2 separate processes: the incentive (BPCA) and requirement (PREA) that are only partially unified
  • EU’s pediatric process is unified under their legislation
  • Timing: European process is asking for information earlier in development
  • Legislation passed in 2012 to facilitate moving the US and Europe closer together in the requirements for timing of discussion of pediatric plans

• Approval from one regulatory body does not guarantee approval from the other
# Common Elements of Pediatric Plans

## US Pediatric Study Plan (PSP)
- **Overview of the disease** in the pediatric population
- Potential plans and justification for use of *extrapolation*
- Plans and justification for *full or partial waiver*
- Plans for pediatric specific *formulation* development
- *Nonclinical data*, complete or planned
- Synopsis/summary of all *pediatric clinical studies* planned
- **Timeline**
- **Agreements with other Health Authorities** (PIP for EMA)

## EU Pediatric Investigation Plan (PIP)

### Electronic form (including Part A)
- **Part B – Overall development**
  - Indication similarities and differences
  - Diagnosis, prevention, treatment
  - Medical needs and benefits
- **Part C – product-specific waivers**
- **Part D – PIP**
  - Indications
  - Pediatric subsets
  - Quality aspects (overall strategy)
  - Non-clinical aspects
  - Clinical aspects
  - Timeline
- **Part E – Deferrals**
IMPLICATIONS FOR PEDIATRIC DRUG DEVELOPMENT
Current Thinking on Relevant Pathways
Pharmacology Matters

Pharm GKB Website
Critical Role of Biodisposition

• The collective combination of ADME determines drug exposure

• Drug exposure determines drug response

• Knowledge of the relationship between PG/PK/PD in order to determine what dose gives the desired exposure and response
The Puzzle Within the Puzzle

• Children are not simply small adults and neonates are not simply small children
• Information on age-dependent differences in physiology can aid in the understanding of pediatric PK and PD
• This knowledge can serve as a useful guide in constructing appropriate therapeutic plans
Physiology Matters

• Even with respect to cancer, children are not “little” adults
• Pediatric subpopulations are not created equal
• Treatment relies on tumor-host interaction that is complex
• Multiple factors affect tumor responsiveness
• Makes prediction of treatment success even more difficult
Differences in Toxicity

- Significantly greater incidence of neurotoxicity in infants and young children with vincristine
- Increased hepatoxicity for actinomycin D
- Increased ototoxicity for cisplatin
- Increased anthracycline-related cardiotoxicity and mucositis
- Increased ifosfamide-related nephrotoxicity and rickets

Some of these differences disappear with weight based dosing in younger children
Pediatric Formulation Considerations

### Softgels

<table>
<thead>
<tr>
<th>Size</th>
<th>Shell Material</th>
<th>Stabilizers</th>
<th>Anticaking Agents</th>
<th>Solubility Enhancers</th>
<th>Polymers</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 Oval</td>
<td>Form the capsule body to fill required material (Gelatin, Type A and B)</td>
<td>Imparts, softness, elasticity, hardness to capsule shell (Glycerol (85% &amp; 98%))</td>
<td>Prevent clumping and sticking of granules on punches (Polyethylene glycol)</td>
<td>Increase disintegration rate of filling content to up the action (Sodium croscarmellose)</td>
<td>Control the rate of dissolution of drug candidate (HPMC)</td>
</tr>
<tr>
<td>5 Oval</td>
<td></td>
<td></td>
<td>Prevent dusting that results from automatic capsuling (Inert edible oils)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.5 Oval</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Tablets

<table>
<thead>
<tr>
<th>Size</th>
<th>Shell Material</th>
<th>Stabilizers</th>
<th>Anticaking Agents</th>
<th>Solubility Enhancers</th>
<th>Polymers</th>
</tr>
</thead>
<tbody>
<tr>
<td>7/16 x 0.358</td>
<td>Form the tablet body to fill required material (Maltose)</td>
<td>Prevent clumping and sticking of granules on punches (Polyethylene glycol)</td>
<td>Prevent dusting that results from automatic capsuling (Inert edible oils)</td>
<td>Increase disintegration rate of filling content to up the action (Sodium croscarmellose)</td>
<td>Control the rate of dissolution of drug candidate (HPMC)</td>
</tr>
<tr>
<td>3/16 x 0.600</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Capsules

<table>
<thead>
<tr>
<th>Size</th>
<th>Shell Material</th>
<th>Stabilizers</th>
<th>Anticaking Agents</th>
<th>Solubility Enhancers</th>
<th>Polymers</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;00&quot;</td>
<td>Form the capsule body to fill required material (Gelatin, Type A and B)</td>
<td>Imparts, softness, elasticity, hardness to capsule shell (Glycerol (85% &amp; 98%))</td>
<td>Prevent clumping and sticking of granules on punches (Polyethylene glycol)</td>
<td>Increase disintegration rate of filling content to up the action (Sodium croscarmellose)</td>
<td>Control the rate of dissolution of drug candidate (HPMC)</td>
</tr>
<tr>
<td>&quot;0&quot;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&quot;1&quot;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Excipients used in capsule dosage form

- Shell material
- Stabilizers
- Anticaking Agents
- Solubility Enhancers
- Polymers
## Adult Dosage Forms in Children?

<table>
<thead>
<tr>
<th>Route of Administration</th>
<th>Dosage Form</th>
<th>Characteristic &amp; Related Issue for Paediatric Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>Tablets &amp; Capsules</td>
<td>Size - Swallowability</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dose Strength - Typically too high with fixed strength</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Excipients - Concentrations not tolerated / unknown Tox profile</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Packaging – No child resistant features</td>
</tr>
<tr>
<td>Parenteral</td>
<td>Injections &amp; Infusions</td>
<td>Dose Volume - Too high or too low (accuracy for dispensing)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dose Strength - Typically too high</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Excipients - Concentrations not tolerated / unknown Tox profile</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Administration Site - Painful administration</td>
</tr>
<tr>
<td>Inhalation</td>
<td>Dry Powder Inhalers, Nebulisers, &amp; Pressurized Metered Dose Inhalers</td>
<td>Device - Ability to coordinate inhalation with device activation, long administration time</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dose Strength - Typically too high with fixed strength</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Excipients - Concentrations not tolerated / unknown Tox profile</td>
</tr>
<tr>
<td>Transdermal</td>
<td>Creams, Ointments &amp; Gels</td>
<td>Dose Strength - Typically too high with fixed strength</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Administration Site - Tolerability from API / Excipients (local &amp; systemic)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Excipients - Concentrations not tolerated / unknown Tox profile</td>
</tr>
</tbody>
</table>

Requirements of Pediatric Formulations

• Need to consider age, physical development, illness, dosage, dosing frequency, treatment duration, and route of administration

• Formulation needs to be:
  • Easy to administer and swallow
  • Acceptable for taste
  • Acceptable for volume
  • Appropriate for dosage and strength
  • Tolerable with minimal and safe excipients

• Children will refuse unpleasant formulations

• Administration needs to be safe and precise (including excipients)
IMPLICATIONS FOR PEDIATRIC DRUG DEVELOPMENT
Need for Proactive Pre-clinical Testing

Earlier pre-clinical testing is necessary to better determine appropriate pediatric clinical studies.

Competitive landscape—we need to do this now.

COSTS:
• Cost to develop models or outsource testing
• Unnecessary testing for early phase molecules that fail
• Consortium/KOL meetings to guide evolving model/treatment landscape

BENEFITS:
• Can help evaluate whether a waiver is the best strategy early in the process
• Cost/resource savings in preventing study plans that become irrelevant
• May discover activity in molecules otherwise without utility
What is the PPTC?

A resource to identify target expression and subsequently conduct pre-clinical experiments.
ITCC-P4: The platform

- 400 PDX models/Syrs; GEMMs
- Standard-of-care and targeted compound testing
- POC for immunotherapies in humanized models
- POC for organoids

ITCC-P4 Workflow

- WP 1: Consortium management
- WP 2: Systematic target prioritization/ actionable in pediatric solid tumors
- WP 3A: Model development including alternative models
- WP 3B: Model characterization including cross-species
- WP 4: Regulatory preclinical consensus
- WP 5: Preclinical drug testing in vitro and in vivo
- WP 6: Information management and data analysis
- WP 7: Sustainability and contractual management

Initial compound testing began mid-2019
Need Adaptation of Research Tools

- **First-in-child**
  - Phase 1
  - Develop Pediatric-PRO-CTCAE to improve toxicity reporting in clinical trials

- **Biology driven & improved trial design**
  - Phase 2
  - Innovation in trial design (Bayesian, Adaptive...)

- **Frontline vs SOC**
  - Phase 3
  - OS & EFS as primary endpoints for phase 3
  - Validation of RECIST to strengthen the use of Response

- **Validation with Real World Data**

  **QOL**
  - Validate QoL measurements in children, AYA, and proxies
## Innovative Trials: Extrapolation Approaches

<table>
<thead>
<tr>
<th>Differences between populations</th>
<th>Uncertainty of hypothesis</th>
<th>Extrapolation</th>
<th>Study program (target population)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large</td>
<td>High</td>
<td>No extrapolation</td>
<td>Full development program</td>
</tr>
<tr>
<td>Moderate</td>
<td>Some</td>
<td>Partial extrapolation</td>
<td>Reduced study program dependent on magnitude of expected differences and/or degree of uncertainty</td>
</tr>
<tr>
<td>Small</td>
<td>Low</td>
<td>Full extrapolation</td>
<td>Some supportive data for validation</td>
</tr>
</tbody>
</table>

- PK/PD studies only (including M & S)
- Dose-ranging or dose-titration studies
- Non-controlled 'descriptive' efficacy / safety study
- Controlled study but 'arbitrary' sample size
- Larger significance level, lower %age confidence intervals
- Studies powered on surrogate endpoint
- Intrapolation (bridging)
- Modelling prior information from existing data sets (Bayesian, meta-analytic predictive)
- etc
Is it reasonable to assume that children when compared to adults have similar: (1) similar disease progression? (2) response to intervention?

- NO to either
- YES to both

Is it reasonable to assume similar exposure-response in pediatrics and adults?

- NO
- YES

Is there a PD measurement that can be used to predict efficacy in children?

- NO
- YES

**Conduct:**
1) Adequate dose-ranging studies in children to select dose(s) that achieve similar exposure to adults
2) Safety trials at the identified dose(s) in children

**Footnotes:**
a. For drugs that are systemically active, the relevant measure is systemic concentration.
b. When appropriate, use of modeling and simulation for dose selection (supplemented by pediatric clinical data when necessary) and/or trial simulation is recommended.
c. For locally active drugs, includes plasma PK at the identified dose(s) as part of the safety assessment.
d. For partial extrapolation, one efficacy trial may be sufficient.

IMPLICATIONS FOR PEDIATRIC DRUG DEVELOPMENT
Questions?