Best Pharmaceuticals for Children Act (BPCA)

Written Requests for Oncology Products

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Goals of a Pediatric Development Program

- Obtain evidence based data to support the dosing, safety, and efficacy of products intended for use in the pediatric population
- Communicate this information in the product labeling to allow judicious use of the drug in the indicated population

Pediatric product development should be integrated into the adult development program and not be an afterthought.

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1902 Biologics Control Act
1906 Pure Food and Drug Act
1938 Food Drug and Cosmetic Act
1962 Kefauver-Harris Amendment

Early pediatric legislation reflected a response to products that caused harm.

Later pediatric legislation encourages pediatric investigations to inform product labeling.

1979 *Pediatric Use* Subsection under *Precautions*

1997 FDAMA/Pediatric exclusivity provision

2002 Best Pharmaceuticals for Children Act (BPCA)

2003 Pediatric Research Equity Act (PREA)

2007 Food & Drug Administration Amendments Act (FDAAA)

2012 FDA Safety and Innovation Act (FDASIA)

2017 FDA Reauthorization Act (FDARA)

- PREA amended to require pediatric assessments of drugs directed at molecular targets considered relevant in pediatric cancer regardless of the adult indication; removes orphan exemption

Best Pharmaceuticals for Children Act (BPCA)

- Provides a financial incentive to VOLUNTARILY conduct pediatric studies of a product under a Written Request (WR)
- A WR document specifies the details of the pediatric studies to be completed in order to receive the financial incentive (pediatric exclusivity).
- A sponsor may request the FDA to issue a WR by submission of a Proposed Pediatric Study Request (PPSR) **OR** FDA may issue a WR without a PPSR.
- PPSR should contain rationale for studies, detailed study designs and plans for formulation development

BPCA: Pediatric Exclusivity

- Applicants who fulfill the terms of a WR are eligible to receive pediatric exclusivity.
  - Additional 6 months of exclusivity
  - Exclusivity attaches to all existing marketing exclusivities and patents for the drug moiety.
  - Pediatric exclusivity does not require positive pediatric studies or granting a new indication.

Question: How many drugs have been approved for a pediatric cancer based on studies conducted under a Written Request?

- A: 2
- B: 17
- C: 0
- D: 9

BPCA facilitates Pediatric Oncology Drug Development

- Written Requests are the primary regulatory mechanism under BPCA for obtaining data for pediatric cancer drug approvals and product labeling.
- Since enactment of pediatric exclusivity legislation:
  - **70** WRs issued by OHOP
  - 9 drugs have been approved for pediatric cancer indications supported by studies conducted under a WR.
  - 17 products have had pediatric safety/dosing information added to the label.
  - 24 products have been granted exclusivity.
  - More than 30 products are currently being investigated under WR/BPCA.

Products with a pediatric oncology indication based on studies conducted under a WR

DRUG	CONDITION STUDIED UNDER WR
Blinatumomab	ALL
Clofarabine*	Refractory ALL
Dasatinib	Ph+ CML in the chronic phase
Everolimus	SEGA
Imatinib	Ph+ ALL and Ph+ CML
Ipilimumab	Unresectable or metastatic melanoma (≥ 12 years)
Larotrectinib*	Metastatic or refractory solid tumors with NTRK gene fusion
Nilotinib	Ph+ CML, relpased or refractory Ph+ ALL
Tisagenlecleucel*	Relapsed or refractory ALL

Products with pediatric information added to label based on a WR

DRUG	CONDITIONS STUDIED UNDER WR
Bendamustine	Relapsed or refractory ALL and AML
Bortezomib	Relapsed ALL
Busulfan	Bone marrow transplant
Cabazitaxel	High-grade glioma and DIPG
Capecitabine	Newly diagnosed non-disseminated DIPG, HGG
Carboplatin	Refractory or relapsed malignancy
Docetaxel	Refractory or relapsed solid tumors
Erlotinib	Refractory or relapsed ependymoma
Fludarabine	Refractory acute leukemia
Gemcitabine	Relapsed or refractory acute lymphoblastic leukemia
Irinotecan	Refractory or relapsed solid tumors; newly diagnosed metastatic RMS
Ixabepilone	Advanced or refractory solid tumors
Oxaliplatin	Refractory or relapsed solid tumors
Pemetrexed	Refractory or relapsed solid tumors
Temsirolimus	Refractory or relapsed solid tumors; NBL, RMS, HGG
Trabectedin	Histotypes of sarcoma, predominantly RMS, osteosarcoma, Ewing sarcoma, and non-RMS STS
Vinorelbine	Leukemia or refractory or relapsed solid tumors

Pediatric Labeling: (not so distant) Past and Present

Label Section	Asparaginase (Elspar)-2002	Tisagenlecleucel (Kymriah; CAR T-Cell)-2017
Indications and Usage	"in the therapy of patients with ALL…useful primarily in combination with other chemotherapeutic agents in the induction of remissions… in pediatric patients"	"for the treatment of patients up to 25 years of age with B-cell precursor ALL that is refractory or in second or later relapse"

Pediatric Labeling: (not so distant) Past and Present

Label Section	Asparaginase (Elspar)-2002	Tisagenlecleucel (Kymriah; CAR T-Cell)-2017
Pediatric Use	"Asparaginase toxicity is reported to be greater in adults than in pediatric patients."	"The safety and efficacy of KYMRIAH have been established in pediatric patients with r/r B-cell ALL. Use of KYMRIAH is supported by a single-arm trial that included 52 pediatric patients with r/r B-cell precursor ALL in the following age groups: 33 children (age 3 years to less than 12 years) and 19 adolescents (age 12 years to less than 17 years). No differences in efficacy or safety were observed between the different age subgroups or in comparison to the young adults in the trial. " Reference to Sec 14.

Pediatric Labeling: (not so distant) Past and Present

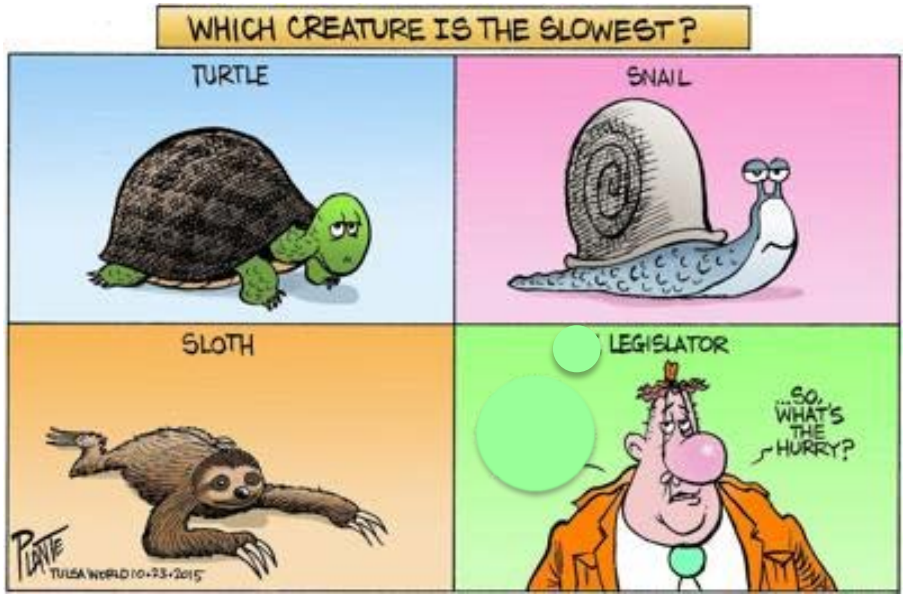
Label Section	Asparaginase (Elspar)-2002	Tisagenlecleucel (Kymriah; CAR T-Cell)-2017
Clinical Studies	No description	The efficacy of KYMRIAH in pediatric and young adults with r/r B-cell precursor ALL was evaluated in an open-label, multicenter single-arm trial …107 patients were screened, 88 were enrolled, 68 were treated, and 63 were evaluable for efficacy." The 63 evaluable patients included …" age/gender/ethnicity/prior tx "The efficacy of KYMRIAH was established on the basis of…" "Among the 63 infused patients…", time to onset of remission, SCT rate Table summarizing efficacy results

Pediatric Subcommittee of the Oncologic Drugs Advisory Committee (ODAC)

- Industry sponsors obtain input from key academic and community opinion leaders regarding ongoing or potential pediatric development programs.
  - Gauge investigator interest in pediatric investigation of products in various stages of adult development
  - Provide feedback to industry on trial design, study population, pediatric regulations
  - **Discuss drug candidates for a Written Request**

- Interactive discussion of key and relevant topics
  - Immunotherapeutics, PRO instruments, FDARA legislation
- FDA invites sponsors of specific products early in development AND sponsors are encouraged to seek an invitation if there are questions regarding their pediatric development program.

Thanks!


WHICH CREATURE IS THE SLOWEST?
TURTLE
SNAIL
SLOTH
LEGISLATOR
...SO, WHAT'S THE HURRY?
PLAVE
TULSA WORLD 10-23-2015