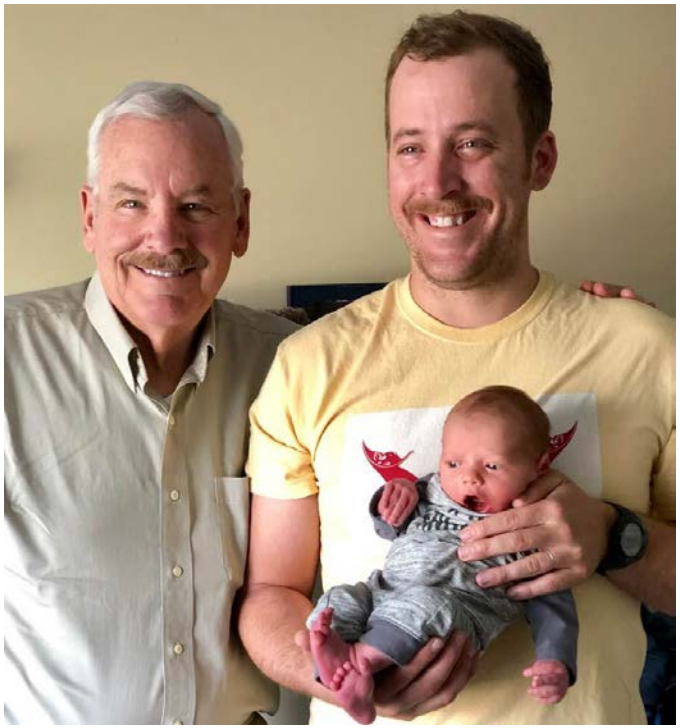
# Special Considerations for Labeling in Pediatric Oncology



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# Current State in Pediatrics

- Majority of children with cancer are treated in academic medical centers on clinical trial protocols
  - All pediatric oncology trials are essentially multi-agent, multi-year
  - Increasing international efforts

- Clinical trials are the GOLD standard in pediatrics
  - Randomized trials are thought to be of the highest value
  - Non-inferiority trials are rare in pediatrics

- Most children are treated “off label” due to a paucity of agents actually approved in pediatric cancer

- Level of evidence for availability and use depends on current technology and adult data/experience, as well as availability of drugs for pediatric use

# Current State in Pediatric Oncology

- Relationship between FDA and pediatric oncologists is generally very positive and interactive

- Despite regulatory “wins” there is less incentive to develop drugs for pediatrics overall
  - Small market share / hard to recoup costs
  - Generics are probably even less incentivized in the current environment

# Chemotherapy Agents Used in Childhood ALL by year of US FDA Approval

- 6-Mercaptopurine 1953
- Methotrexate 1953
- Prednisone 1955
- Dexamethasone 1958
- Cyclophosphamide 1959
- Vincristine 1964
- Cytosine arabinoside 1969
- L-Asparaginase 1978
- Daunorubicin 1979
- Teniposide 1979

- Clofarabine 2004
- Blinatumomab 2014, 2016, 2018
- Tisagenlecleucel 2017

# Major Considerations for Drug Development

- Mechanism of Action
- Agent and formulation availability for peds
- Expected toxicities and CNS penetration
- Preclinical and clinical data availability
  - In the same disease or another ?
  - In adults or children?
- New endpoints would likely need to be consider for generic labels
  - Does = PK mean = response outcome ?

# Scientific Barriers to Pediatric Oncology Generic/Bioequivalent Drug Development

- Drug metabolism frequently varies by age
  - Myriad variables
  - Age cohorts
    - Infant metabolism very different, usually minimal to no data
  - PK / PD data:  when does physiology = adult ?

- Requirements for PK studies for approval yet in many peds studies, PK are “optional” and therefore data are scarce

- Pediatric-friendly formulations are not always available even for brand drugs and are expensive to develop, require additional testing and manufacturing, which subsequently delays access

# Example of an age agnostic label:

**BLINCYTO® (blinatumomab) for injection, for intravenous use**
**Initial U.S. Approval: 2014**

**WARNING: CYTOKINE RELEASE SYNDROME and NEUROLOGICAL TOXICITIES**
***See full prescribing information for complete boxed warning.***

- **Cytokine Release Syndrome (CRS), which may be life-threatening or fatal, occurred in patients receiving BLINCYTO. Interrupt or discontinue BLINCYTO as recommended. (2.3, 5.1)**
- **Neurological toxicities, which may be severe, life-threatening, or fatal, occurred in patients receiving BLINCYTO. Interrupt or discontinue BLINCYTO as recommended. (2.3, 5.2)**

**----------RECENT MAJOR CHANGES----------**

| | |
|---|---|
| Indications and Usage (1) | 3/2018 |
| Dosage and Administration, Treatment of MRD-positive B-cell Precursor ALL (2.1) | 3/2018 |
| Dosage and Administration, Dosage (2.2), Treatment of Relapsed or Refractory B-cell Precursor ALL | 7/2017 |
| Dosage and Administration (2.2, 2.4, 2.5, 2.6, 2.7) | 5/2017 |
| Warnings and Precautions (5.1, 5.2, 5.3, 5.7, 5.12) | 3/2018 |

**----------INDICATIONS AND USAGE----------**

BLINCYTO is a bispecific CD19-directed CD3 T-cell engager indicated for the treatment of adults and children with:

- B-cell precursor acute lymphoblastic leukemia (ALL) in first or second complete remission with minimal residual disease (MRD) greater than or equal to 0.1%. This indication is approved under accelerated approval based on MRD response rate and hematological relapse-free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials. (1.1)
- Relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL). (1.2)

- adult and pediatric
- disease-specific, biologically driven
  - dosing available across age spectrum
- frequent updates

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# Reasons to be Optimistic

- Newer legislation and incentives aim to improve incentives to conduct pediatric studies
  - Expectations should be realistic

- Pediatricians often use drugs off-label anyway so they are not daunted by lack of approval

- Newer approvals for brand names and newer applications – what can we extrapolate from adult studies ?
  - Example: approvals that are (nearly) age agnostic
  - Example: pembrolizumab approval is tumor-type agnostic, biologically driven