Pediatric Subcommittee of the Oncologic Drugs Advisory Committee Meeting May 11, 2022

Developing a Consistent Conceptual Framework to Address Waivers of Pediatric Studies Required by the RACE for Children Act

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RACE for Children Act

- Incorporated as Title V Sec. 504 of the **FDA Reauthorization Act (FDARA),** enacted August 18, 2017
- Amends Pediatric Research Equity Act (**PREA)**(Sec. 505B of the Federal Food, Drug, and Cosmetic Act) **effective August 18, 2020**
- **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" when the subject of an initial New Drug Application (NDA) or Biologic License Application (BLA).
- **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)].
- Study to be described in Agreed Initial Pediatric Study Plan (**iPSP**) and data to be included as part of planned application.
- Elimination of **orphan exemption for pediatric studies** for cancer drugs directed at relevant molecular targets.

Positive Implications of the RACE for Children Act

- Altered the regulatory landscape for cancer drug development for children
- Global impact, in part, due to closer alignment of decisions/timelines of EMA Pediatric Investigation Plans (PIPs) and FDA initial pediatric study plans (iPSPs)
- 70% of Agreed iPSPs since August 2020 for products directed at a **relevant** molecular target; include planned pediatric investigations (25% in progress)
- **86%** of approved New Molecular Entities (NMEs) for cancer* in 2021 have planned/ongoing pediatric investigations compared to 44% in 2020 and 14% in 2019

  * directed at a relevant molecular target

Waiver Considerations for Agents Directed at Relevant Targets

- Serious known or expected developmental toxicity- consideration for **full or age dependent partial waiver**
- Feasibility and practicability due to small study populations potentially addressed by limited study requirements and innovative study designs
- Partial (age-dependent) waivers: disease incidence and available formulations

The anticipated, but unintended consequence of required early studies

- Multiple “in class” products (**single agent**) without compelling evidence of substantial differences in efficacy, safety, pharmacokinetic (PK profiles), or formulation to warrant additional pediatric studies **16 agreed plans for full waivers for same in class 8/18/20 to date**

FDARA Implementation Guidance for Pediatric Studies of Molecularly Targeted Oncology Drugs: Amendments to Sec. 505B of the FD&C Act Guidance for Industry

Waivers:

- For studies of subsequently developed (i.e., later-generation) products with the identical mechanism of action when ongoing, competing studies in the pediatric population are being or have been conducted and when there is no convincing evidence that the new active ingredient would provide a superior pharmacologic, toxicity, or activity profile when compared to products with the same molecular mechanism of action already studied or under investigation, potentially resulting in a very small number of patients available to participate in a new investigation.

- When a drug or drugs with the same mechanism of action directed at the same molecular target expressed in the same cancer(s) in children has/have failed to demonstrate evidence of activity.

Expectations

- Discussion of critical variables to guide decisions regarding planned waivers; extent of information (including comparisons of products when possible) required to be included in iPSP by sponsor
- Clinical activity (adult/pediatric)
- Non-clinical considerations
- Pharmacology considerations including central nervous system (CNS) penetrance
- Product quality/formulations
- Not intended to focus on **prioritization** of products for ultimate pediatric development, although principles may be closely related, but timing required for iPSP agreement precludes this consideration; other multi-stakeholder platforms exist to serve this purpose
- Consistency and Transparency are critical to these considerations and decisions.
- Outcome focused exclusively on **optimal use of the authority provided by amended PREA provisions to benefit children with cancer**


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Scope of the Current Problem: Examples of Multiple Same in Class Products for Hematologic Malignancies

Meeting of the Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee
May 11, 2022

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Initial Pediatric Study Plan (iPSP) Requirements Post - FDARA

- Pediatric assessments are to be submitted for an original NDA or BLA unless the requirement is waived or deferred if the drug is:
  - Intended for the treatment of an adult cancer
  - Directed at a molecular target substantially relevant to the growth or progression of a pediatric cancer
- iPSP submission not later than 60 days after the EOP2 meeting or no later than 210 days prior to submission of the NDA/BLA
- Report should contain data on safety, dosing and preliminary assessment of efficacy in pediatrics

Abbreviations: NDA – New Drug Application, BLA – Biologics License Application, FDARA – Food and Drug Administration Act of 2017, EOP2 – End of Phase 2

A “Good” Problem

- Rapid development of products directed at molecular targets for adult hematologic malignancies (CLL, MM, NHL)
- Multiple Agents → few pediatric patients
- Waiver for Same in Class Agents may be justified for **later-generation products with identical mechanism of action (MOA)**
  - Competing pediatric studies are **ongoing or have been conducted** and no evidence of clear **advantage**
  - Data from prior studies conducted on an agent with same MOA have **failed to demonstrate activity**

Abbreviations: CLL – Chronic Lymphocytic Leukemia, MM-Multiple Myeloma, NHL-non-Hodgkin Lymphoma

Additional Considerations
Same-in-Class Waivers

- **Advantage**
  - Improved activity
  - Favorable safety profile
  - Pediatric formulations (e.g. oral vs Intravenous) - ease of administration
  - PK considerations (e.g. Central Nervous System (CNS) penetration
- **Evolving Data: Waiver vs. Deferral**
  - Safety and Efficacy from adult or other pediatric studies
  - Subpopulation considerations (biomarker positive)
  - Dose optimization
- **Optimal agent vs. first agent (timing)**
  - Prioritization by cooperative groups

Same-in-Class Waiver Consideration
DHM2 2021-2022
Examples

- Bruton Tyrosine Kinase inhibitors (BTKi) **(7)**
- Phosphatidylinositol 3 Kinase inhibitors (PI3Ki) **(9)**
- CD20–CD3 T-Cell Bispecific Antibodies (TCB) **(4)**

Bruton Tyrosine Kinase Inhibitors (BTKis)

- Development/approvals in Adult B-cell NHL
- 3 Agents approved - pre-FDARA, no required pediatric studies
- One Study conducted under Written Request – efficacy not demonstrated*

Post-FDARA BTKis in Development

Products Adult Indications	iPSP proposal	Agency Decision	Rationale	Additional Considerations
4 Products R/R NHL CLL/SLL including PCNSL	**Full Waiver**	General **Agreement** with plan to request full waiver for pediatric studies	• Activity not demonstrated for same in class agent • No apparent advantage • Efficacy considerations in adult aggressive lymphoma • Not prioritized for peds	Requirement to address pediatric CNS lymphoma in iPSP

Abbreviations: R/R NHL Relapsed or Refractory non-Hodgkin Lymphoma CLL – Chronic Lymphocytic Leukemia, SLL- Small Lymphocytic Leukemia, PCNSL – Primary Central Nervous System Lymphoma

*Burke et.al, *Leukemia*, 2020; Burke et. al, ASPHO 2021

Phosphoinositide -3 Kinase inhibitors (PI3Ki)

- Development in adult B-cell indolent NHL (FL, MZL, CLL/SLL)
- Potential relevance for pediatric B-cell malignancies and solid tumors
- 4 Agents approved* (pre FDARA) for adults with CLL/FL/MZL – pediatric studies not required
  - One agent evaluated in pediatric COG study under WR (IV formulation)

Post-FDARA PI3Kis in Development

Products Adult Indications	iPSP proposal	Agency Decision	Rationale	Comments
Product A R/R NHL	**Full Waiver**	**No Agreement** with plan for Waiver	• 1st post FDARA iPSP for class • Potential advantage - oral formulation	• Isoform Considerations • Safety and dose optimization considerations
Product B and C R/R NHL		**General Agreement** with Plan to request full waiver for pediatric studies	• No advantage over same-in-class • Not prioritized • Competing ongoing study	

Abbreviations: NHL non-Hodgkin Lymphoma, FL – Follicular Lymphoma, MZL Marginal Zone Lymphoma CLL – Chronic Lymphocytic Leukemia, SLL- Small Lymphocytic Leukemia, COG – Children's Oncology Group, WR – Written Request, R/R Relapsed or Refractory

*some indications recently withdrawn – toxicity concerns – dose optimization requirements

CD20/CD3 T-Cell Bispecific (TCB)

- Development in adults with CD20 positive B-NHL/No approvals to date
- Potential relevance in pediatric CD20 positive BCL, B-AL, Burkitt's Lymphoma
- Prioritized at ACCELERATE meeting → Platform study **planned**
- Safety considerations – Cytokine Release Syndrome (CRS)

Post-FDARA CD20-TCBs in Development

Products Adult Indication	IPSP proposal	iPSP Agency Decision	Rationale	Comments
4 Products **R/R iNHL** **R/R Aggressive BCL**	Plan to Request Deferral pending platform study Plan for Deferral pending additional data in adults available	• **No agreement for plan for deferral pending platform study** • Agreement in with a plan for deferral for additional safety data in adults (CRS)	Unclear start time for platform study Delay pending safety data in adults for some agents justified	Planned Platform study Consideration for monotherapy and combination therapy regimens Discussion with other regulatory bodies

Abbreviations: BCL – B cell Lymphoma, B-AL - B-cell Acute Leukemia, FL – Follicular Lymphoma, iNHL – indolent non-Hodgkin Lymphoma

Cooperative Group/Platform Studies

- May be acceptable to include in iPSP but must be agreed upon and ongoing or soon-to-be-initiated
- Responsibility rests with the sponsor, cannot rely on plan for cooperative group
- An *ongoing* platform study evaluating targeted agent may be justification for a waiver for same-in-class agents

Summary

- Plans to request Same-in-Class Waivers are common and likely to continue
- DHM2 experience highlights need for early planning, coordination and cooperative group considerations
  - Sponsor – Cooperative Group/Academic interaction encouraged early
  - Regulatory Agency Alignment pursued when feasible
  - Prioritization of same-in-class agents for pediatric studies should be guided by science but will be also be influenced by timing
- Consideration for deferral vs. waiver for agents early in development


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Molecularly targeted cancer drugs and biologics

Non-Clinical Studies in Decision-Making Related to Pediatric Investigations

FDA Perspective

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Meeting of the Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee – May 11, 2022

Outline

- Background; nonclinical studies
  - in support of indications in adult patients with cancer
  - in support of indications in pediatric patients with cancer
- Nonclinical studies to guide in decision making on pediatric studies, when the investigational drug inhibits a molecule/antigen and there are other drugs against the same target

Nonclinical studies in support of first-in-human studies in adult (and pediatric) indications

In vitro and in vivo (animal) studies

- Pharmacology, e.g.: mechanism of action, proof-of-concept (PoC)
- Pharmacokinetics (PK)
- General toxicology studies
  - To evaluate on-target (off-tumor) and off-target adverse effects
  - To assist in patient monitoring
  - To assist in first-in-human (FIH) dose selection

See ICH S9 and ICH S9 Questions and Answers for additional information

Nonclinical studies in support of first-in-pediatric (FIP) studies

Keeping in mind that:
The molecular target has been already determined to be relevant in a pediatric cancer, and
Data in adult patients are often available

- **Nonclinical studies are typically limited to :**
  - **Proof-of-concept (PoC)/ pharmacology studies**

    Can help with an optimal trial design
    - Evaluate the activity of drug
    - Evaluate schedule-dependent effects
    - Could be comparative, e.g. with arms of approved drugs

How to ensure safety in FIP studies?

An integrated risk assessment (weight-of-evidence; WoE) based on the totality of data that incorporate:

- Data from clinical studies conducted in adult patients,
- Data from of nonclinical safety studies conducted in support of studies in adult patients,
- Other, e.g.: safety implication based on the mechanism of action (MOA) of the drug

Nonclinical studies to help in the decision making related to pediatric investigation:

when there are multiple drugs against that target

Proof-of-concept (PoC)/ pharmacology studies:

- Comparative pharmacology studies:
  - Comparative binding and activity
    While will not be a safety/ toxicity study, it may provide information on relative tolerability

Other data may be needed to assist with the decision making, e.g.:

- *Comparative PK, as applicable (e.g. when the investigational product is a modified version of an approved product)*

Examples

- IND submitted for Product mAb1, an IgG4 antibody against target X
- Nonclinical (pharmacology, toxicology, PK) studies of mAb1 conducted in support of adult indications. Data in adult patients are available.
- Target X is relevant in a pediatric cancer
- Two IgG4 antibodies approved against X (mAb2, mAb3); pediatric data available in that cancer
- Comparative binding and activity data show mAb1 is comparable to mAb2 and mAb3
  - May point to comparable safety, in conjunction with other data
- The clinical team may decide that a study in children for that specific cancer is not warranted

- IND submitted for Product mAb1, an IgG1 antibody against target X
- Nonclinical (pharmacology, toxicology, PK) studies of mAb1 conducted in support of adult indications. . Data in adult patients are available.
- Target X is relevant in a pediatric cancer
- Two IgG4 antibodies approved against X (mAb2, mAb3); pediatric data available in that cancer
- Comparative pharmacology data show increased activity of mAb1 compared to mAb2 and mAb3
  - Indicates potential differences in safety
- The clinical team may decide that a study in children for that specific cancer is warranted


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Meeting of the Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee

Clinical Pharmacology Considerations for Same-In-Class Products

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May 11, 2022

Outline

- Physiological differences observed in pediatric patients
- Selecting dosage form for relevant pediatric age groups
- Identifying dosing regimen for pediatric patients
- Summary

Multiple Physiologic Alterations Observed in Pediatric Patients

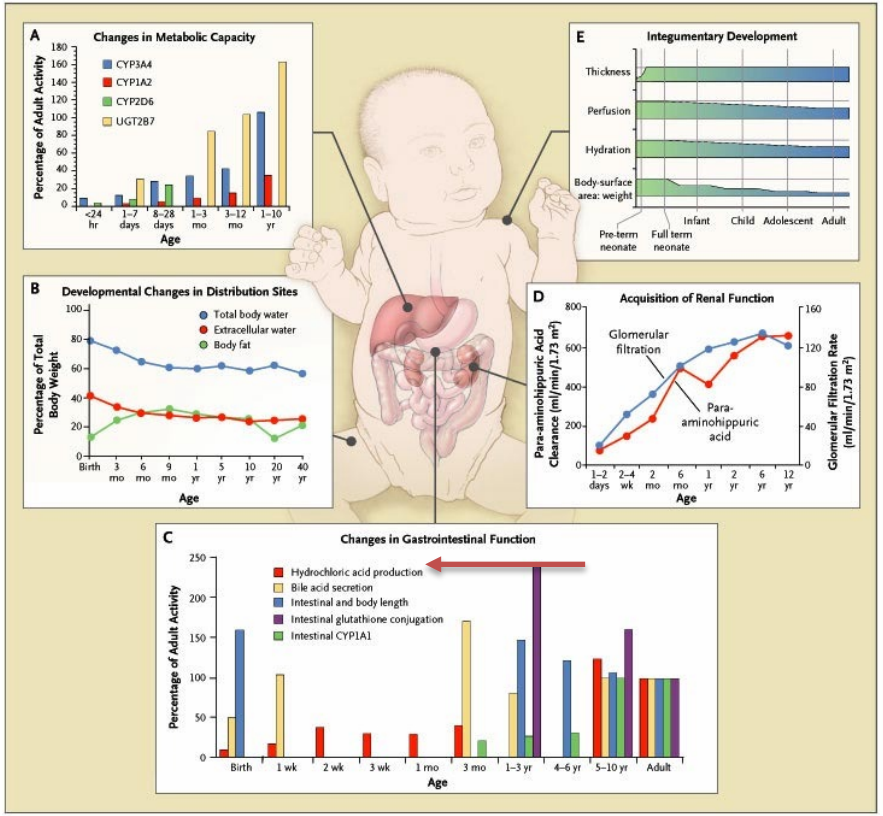
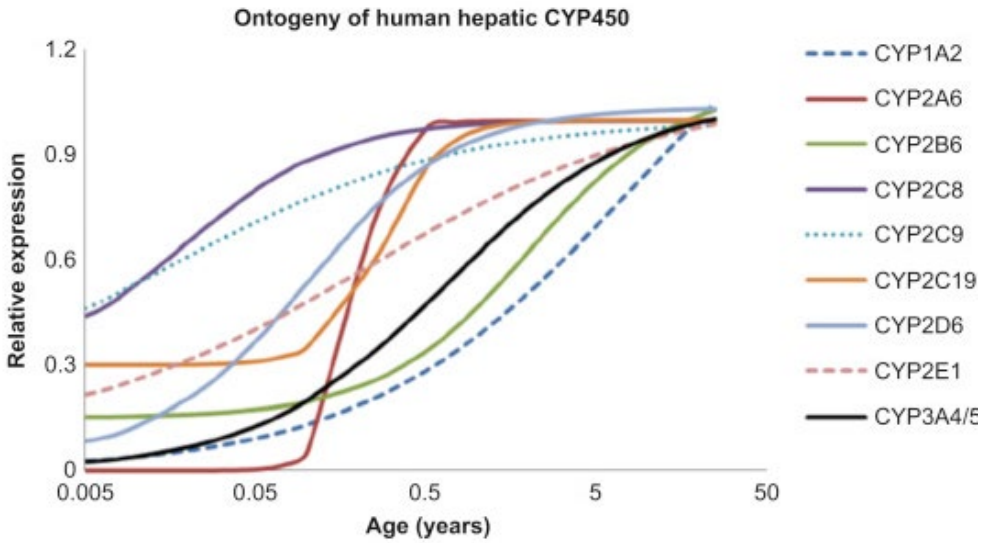


Figure from Kearns et al.
N Engl J Med
2003;349:1157

Physiological Alterations: Major Cytochrome P450 Lower Expression in Some Pediatric Age Groups



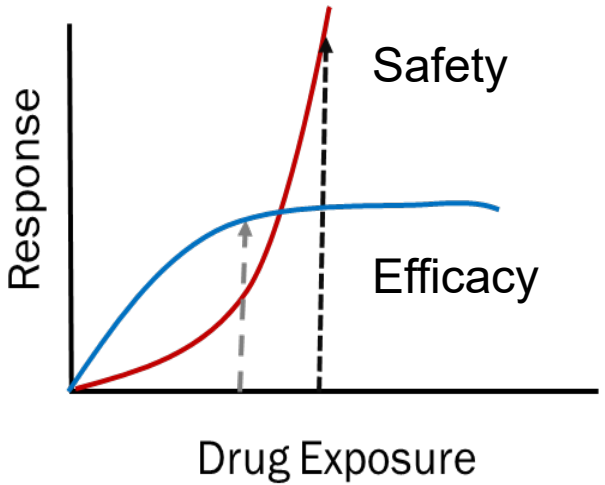
- Cytochrome P450 enzymes reach adult values at different ages
- Reduced metabolism may have clinically meaningful effect on
  - safety (i.e., not clearing drug) or
  - effectiveness (i.e., not making active metabolite)

Photo courtesy of https://www.sciencedirect.com/science/article/pii/B9780128029497000080

How These Physiological Alterations Affect Drug Exposure

- Can lead to differences in pharmacokinetics, which could impact
  - Safety
  - Effectiveness

- Could also affect the impact of the following on drug exposure:
  - Food effect
  - Drug interaction
  - Organ impairment



When Comparing Same-In-Class Drugs

	Drug A	Drug B	Drug C	Drug D	Drug E
Dosage and Administration	Twice daily with or without food	Once daily with food	Twice daily with food	Once daily with or without food	Once daily with or without food
Dosage Modifications for Organ Impairment	Moderate & severe hepatic Severe renal	Severe hepatic Severe renal – NOT studied	Severe hepatic Severe renal – NOT studied	Severe hepatic Severe renal	Moderate & severe hepatic – not studied Severe renal
Drug Interactions	Strong & moderate CYP3A inhibitors & strong CYP3A inducers CYPXX substrates	Strong CYP3A inhibitors & inducers CYPXX & CYPXX substrates	None	Strong & moderate CYP3A inhibitors & inducers	Strong & moderate CYP3A inducers [contraindication] Strong CYP3A inhibitors CYPXX and Pgp substrates

When Comparing Same-In-Class Drugs

	Drug A	Drug B	Drug C	Drug D	Drug E
Dosage and Administration	Twice daily with or without food	Once daily with food	Twice daily with food	Once daily with or without food	Once daily with or without food
Dosage Mo for Impairment	Moderate & severe Severe renal	Severe hepatic NOT studied	Severe hepatic NOT studied	Severe hepatic	Moderate & Severe renal
Dr Int					A n]
					CYPXX and Pgp substrates

Drug A developed in pediatric patients. Do these same-in-class drugs suggest a potential advantage to developing in pediatric patients?

- Will pediatric patients prefer to take the drug once or twice daily?
- Will pediatric patients be able to take the drug with food?
- Will pediatric patients have underlying renal or hepatic impairment?
- Will pediatric patients be taking other drugs that may interact with these drugs? These drugs may be taken to manage comorbid illness, adverse reactions, etc.

Pediatric Dosage Forms

- Multiple dosage forms[1]

- Appropriate dosage form depends on relevant pediatric age groups for patient population
  - Intravenous use
  - Oral use:
    - Swallow solid dosage forms
    - Alter solid dosage forms (i.e., crush, cut, open, mix)
    - Alternative dosage forms (i.e., liquids)
  - Other routes: rectal, intramuscular, transdermal

- Other considerations:
  - Taste, appearance
  - Physical and chemical properties

[1] https://www.fda.gov/industry/structured-product-labeling-resources/dosage-forms

Considerations of Pediatric Age Groups

XALKORI (crizotinib)

- For the treatment of pediatrics aged 1 year and older and young adults with relapsed or refractory systemic anaplastic large cell lymphoma that is ALK-positive
- Available as 200 mg and 250 mg capsules (hard gelatin)
- One open-label study conducted in pediatric patients: 3 to 20 years
- Pediatric patients must be able to swallow intact capsules
- Recommended dosage not established for body surface area less than 0.6 m^2

Can the approved drug product be administered to pediatric age groups likely to be enrolled in the trial?

Can the dosage form and strengths accommodate recommended dosage and dosage modifications for adverse reactions, drug interactions and organ impairment in pediatric patients?

Considering Pediatric Age Groups for Pediatric Development Program

RYDAPT (midostaurin)

- In combination with chemotherapy for the treatment of adults with newly diagnosed acute myeloid luekemia who are FLT3 mutation-positive
- Available as 25 mg capsules (liquid filled)
- Two open-label studies conducted in pediatric patients: 6 months to 17 years
  - Pediatric patients less than 5 years old typically cannot swallow solid dosage form
  - Drug product cannot be altered (i.e., opened)
  - Investigational product used in studies

Is an alternative dosage form or route of administration that is appropriate for the pediatric age groups likely to be enrolled in the trial(s) needed?

Considerations for New Dosage Form, New Strength or Alternative Administration

- If a new dosage form or strength or alternative route or method of administration is needed, additional studies may be necessary to inform dosing regimen in pediatric subgroups
  - In vitro studies
  - Compatibility studies (i.e., tubing)
  - Relative bioavailability studies in adults

Pediatric Dosage Selection

- Possible approaches to identifying dosage in pediatric trials
  - Dose finding studies
  - Modeling and simulation (M&S)

- Consider the following when supporting using M&S (i.e., exposure matching) to select pediatric dosage(s)
  - Disease biology in pediatrics vs. adults
  - Exposure- or dose-response relationships for safety & effectiveness
  - Dose based on body size (i.e., weight or body surface area) vs. flat dosing
  - Growth and developmental changes that affect pharmacokinetics
  - Adverse reactions specific to pediatric patients

https://www.fda.gov/media/90358/download

Extrapolation vs. Separate Development

Extrapolation	Separate Development
Drug A	**Drug C**
NME, Oral kinase inhibitor Peds 12+ years & adults Safety & effectiveness established in adequate & well-controlled studies in adults Anticipate disease biology & PK same in peds & adults Age & BW no clinically meaningful effect	NME, Oral kinase inhibitor Peds 3+ years Open-label, single-arm, multi-center trial (dose-finding, efficacy, safety) Mass balance, food effect, organ impairment, drug interactions, Population PK, ER-safety & effectiveness
Drug B	**Drug D**
NME, Intravenous antibody Peds 12+ years & adults Safety & effectiveness established in adequate & well-controlled studies in adults Anticipate disease biology & PK same in peds & adults Age & BW no clinically meaningful effect	Efficacy supplement, Oral kinase inhibitor Peds 1+ year & adults Open-label, single-arm, multi-center trial (dose-finding, efficacy, safety) Population PK, ER-safety & effectiveness

BW body weight; ER exposure-response; NME new molecular entity; PK pharmacokinetics

Extrapolation vs. Separate Development

Extrapolation	Separate Development
Drug A	**Drug C**
E &	
A	
E &	
A	

First-in-class drug developed in pediatric patients.

- Can the indications and usage be expanded into peds for same-in-class drugs with limited or no additional data?
  - Is the disease biology anticipated to be the same in peds and adults?
  - Is the response to the drug anticipated to be the same in peds and adults?
  - Is the pharmacokinetics anticipated to be the same in peds and adults?
  - Are additional adverse reactions anticipated in peds compared to adults (e.g., bone, dental or other effects on growth and development)?

Summary

- When evaluating pediatric development for same-in-class products
  - Determine the relevant pediatric age groups
  - Consider physiologic alterations and possible implications on the pharmacokinetics of the drug
  - Consider the available dosage form & strengths
  - Consider whether adult data can be used to support dosing regimen in pediatric trials or extrapolation of the indication in adults to pediatrics or specific pediatric age groups
- Same-in-class product may have different clinical pharmacology characteristics that support pediatric development of that product(s)

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Central Nervous System Penetration and Pediatric Brain Tumor Considerations for Same-In-Class Products

Meeting of the Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee – May 11, 2022

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U.S. Food & Drug Administration

Outline

- Pharmacology of Central Nervous System (CNS) penetration
- Beyond the Blood:Brain Barrier
- Parameters to assess CNS penetrance
- Conclusions

Same-in-class ≠ same CNS penetration

Table 2. Distribution to mouse brain of osimertinib, gefitinib, rociletinib, and afatinib following oral administration

	Osimertinib	Gefitinib	Rociletinib	Afatinib
Dose (mg/kg)	25	6.25	100	7.5
Plasma C_{max} (μmol/L)	0.82	0.82	3.32	0.14
Brain C_{max} (μmol/L)	2.78	0.17	BLQ	BLQ
Brain/plasma C_{max} ratio	3.41	0.21	<0.08	<0.36

NOTE: Doses equivalent to clinical doses or reported previously.
Abbreviation: BLQ, below limit of quantification (rociletinib 0.25 μmol/L, afatinib 0.05 μmol/L); C_{max}, maximum plasma concentration.

EGFR tyrosine kinase inhibitors

Ballard et al, *Clin Cancer Res,* 2016

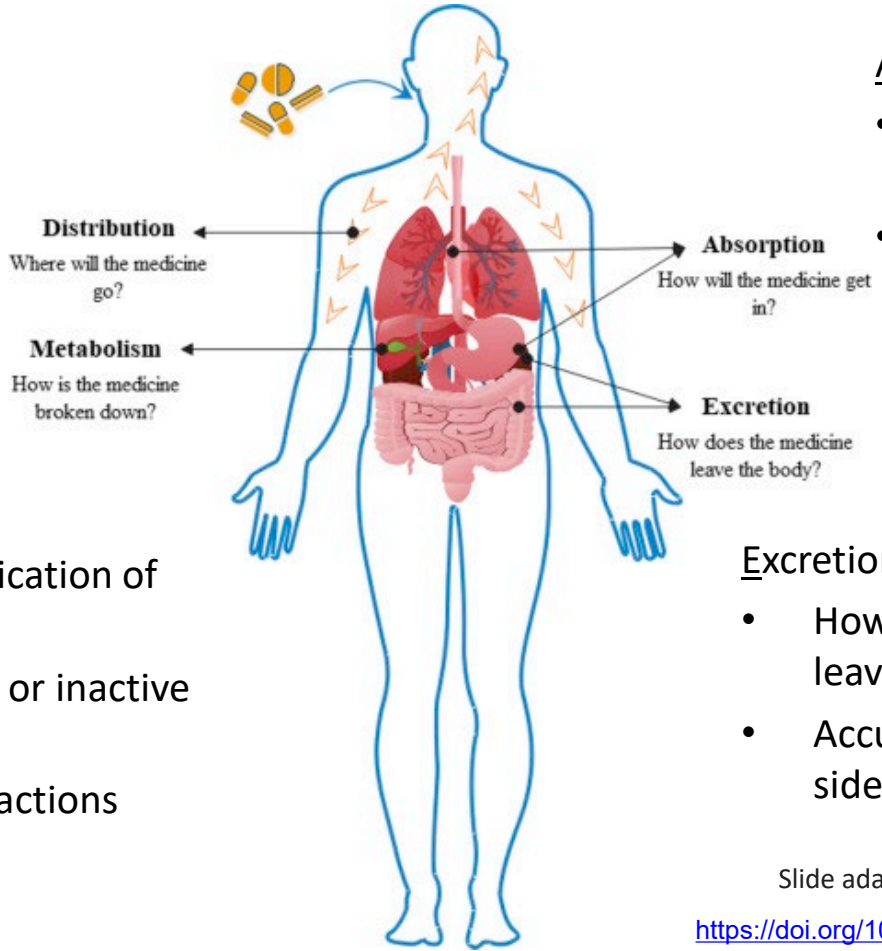
What is the importance of understanding CNS-specific activity?

Unmet medical need for pediatric patients with CNS tumors

Pharmacokinetics: CNS

Distribution

- Movement of drug throughout the body (e.g., brain:plasma concentrations)
- Limitations of measurement in brain



Absorption

- Rate and extent of drug appearance at target site
- Dependent on route of administration and drug substance (size, charge, solubility, lipophilicity, receptor affinity)

Metabolism

- Chemical modification of drug molecule
- Can form active or inactive metabolites
- Drug-drug interactions

Excretion

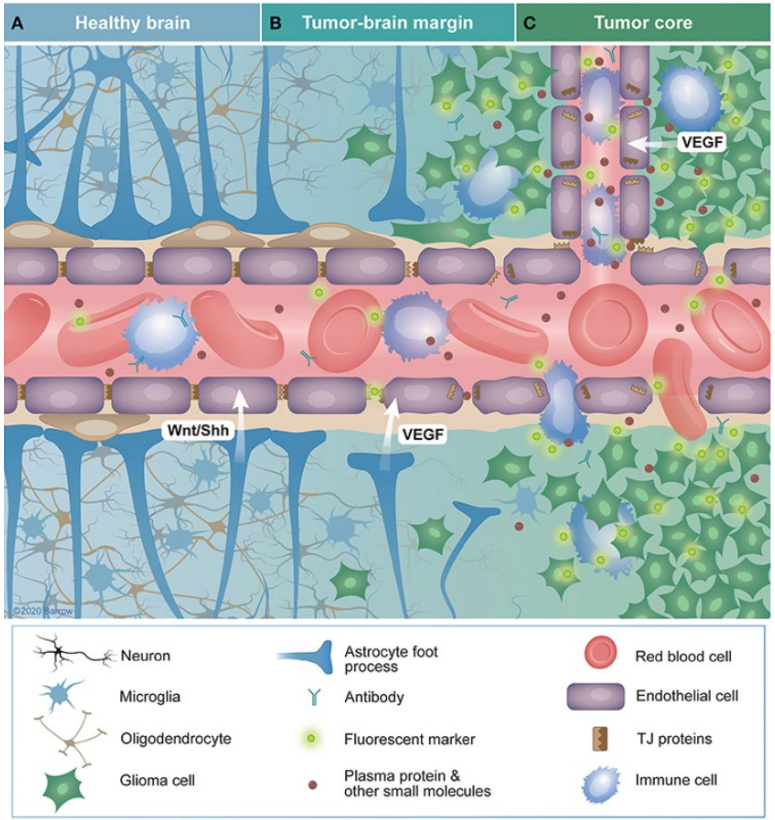
- How drug (and metabolites) leave the body
- Accumulation may lead to side effects

Slide adapted from Lauren Price, PharmD

https://doi.org/10.1016/B978-0-12-814421-3.00021-X

Beyond the Blood:Brain Barrier

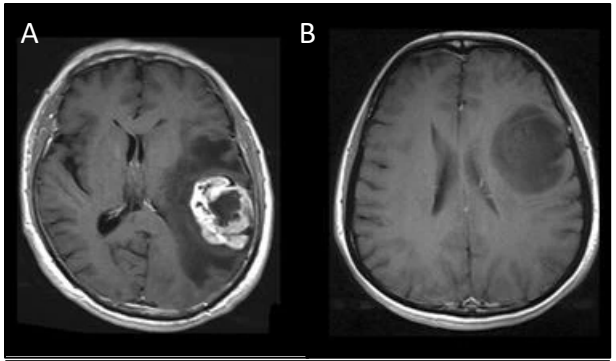
- Structural Barrier
- Metabolically active
- Active transport systems
- Tumor Microenvironment
  - Blood:tumor
  - Blood:Cerebrospinal fluid (CSF)
  - Normal neurons:tumor



Belykh et al, *Front Oncol,* 2020

Beyond the Blood:Brain Barrier

- High-grade brain tumors
  - Secrete soluble factors, cause swelling
  - Magnetic resonance imaging (MRI): contrast enhancement
  - Some tumor still “protected” by intact blood:brain barrier (BBB)

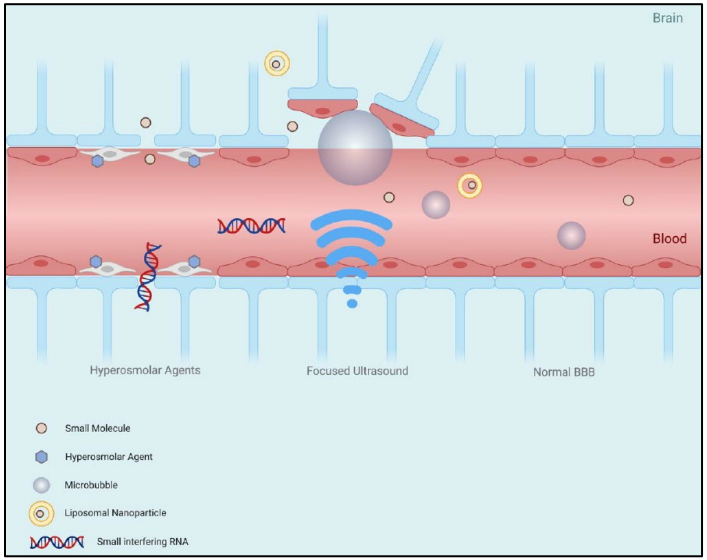


Axial post-contrast T1-weighted MRI; Patient A with high-grade astrocytoma; Patient B with low-grade astrocytoma

Cui et al, *J Neurooncol,* 2014

Beyond the Blood:Brain Barrier

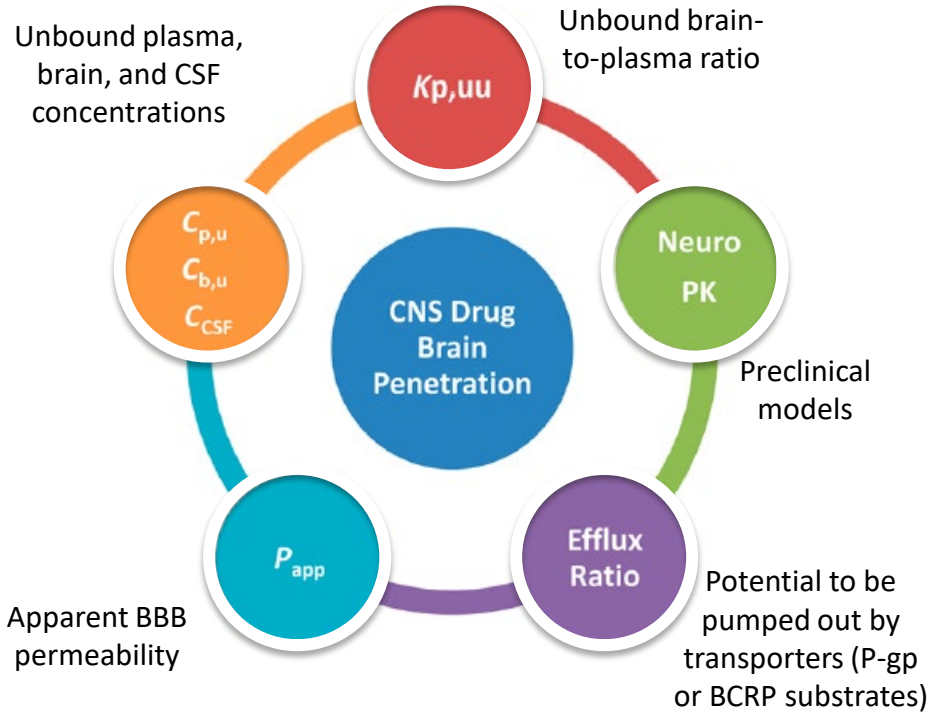
- Direct delivery to CNS
  - Intrathecal
  - Intraventricular
  - Convection-enhanced delivery (CED)
  - Focused ultrasound (FUS)
  - Other devices



Whelan et al, *Pharmaceutics,* 2021

What parameters can be used to assess CNS penetrance?

- In vitro and in vivo models
- Rate of transport (P_{app})
- Efflux ratio
- Extent of brain exposure
  - Brain:plasma ratios
  - CSF:plasma ratios



Di et al, *J Medicinal Chemistry,* 2013

Summary

- There is an unmet medical need for children with brain and spinal tumors
- BBB and CNS penetrance are complex but important to measure
- Same-in-class molecularly targeted agents may have different activity in CNS and should be evaluated as such

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