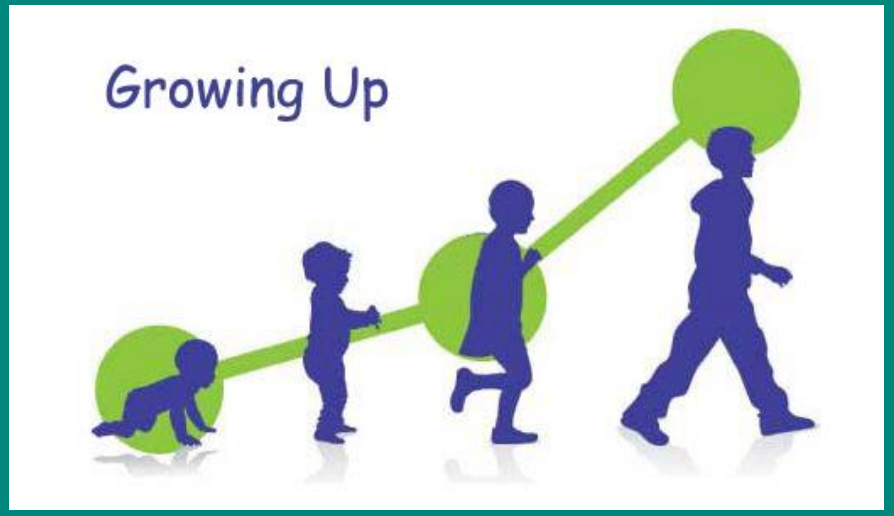
AN INDUSTRY PERSPECTIVE: EVOLUTION IN PEDIATRIC FORMULATION DEVELOPMENT



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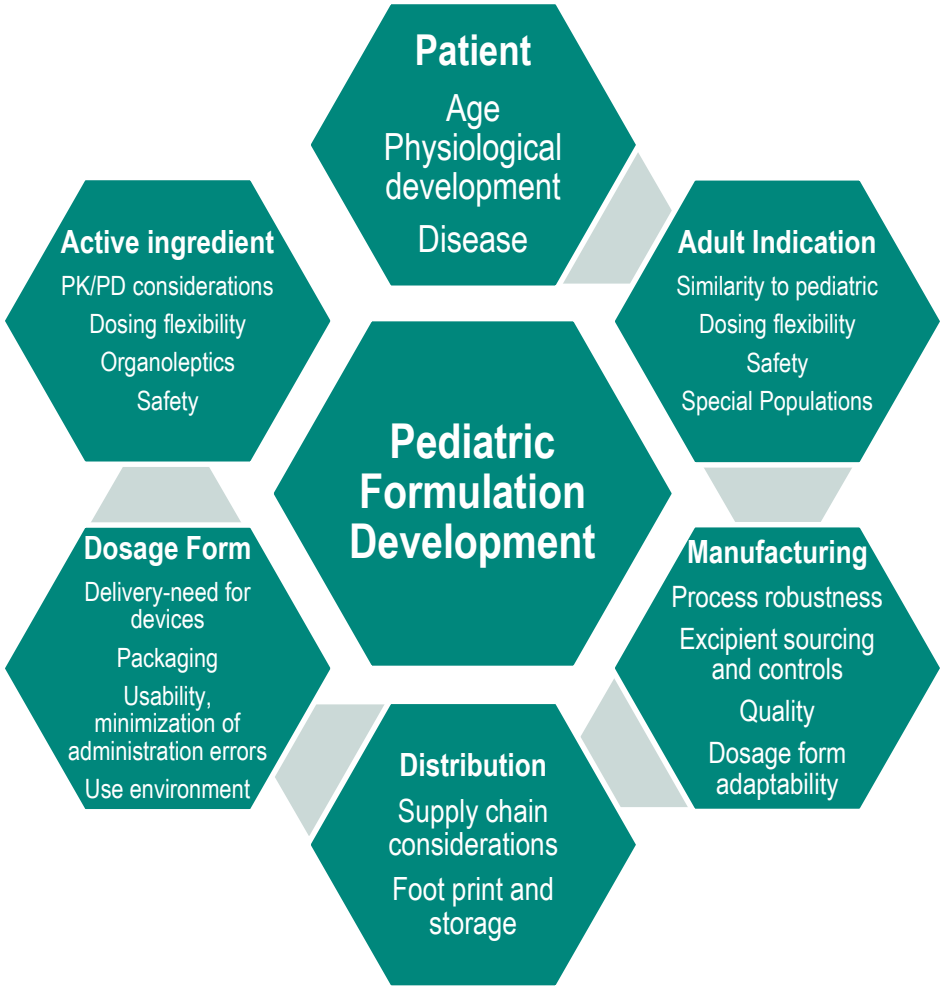
June 2019

Karen C Thompson

Merck & Co, Inc

Multiple Inputs Driving Pediatric Formulation Development.



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Evolution in Age Appropriate Dosage Forms Strickley. JPharm Sci 108(2019)1335-1365

Age	Mass(kg)	Classification	Dosage Forms (current)	Dosage Forms(Proposed)
	<3	Preterm Infant	Nasogastric Tube Solution or suspension (ready to use or powders, granules for constitution	Nasogastric tube using tablets for oral suspension
0-28d	3-5	Newborn Infant	Solution or suspension (ready to use or powders, granules for constitution	Tablets for oral suspension
1 mo-2y	5-10	Infants and toddlers	Solution, suspension, mintiabs, ODT	Mini tablets
2-6y	10-25	Children (preschool)	Mini tabs, ODT, sprinkle powder, oral powder, oral granules	Chewable tablets, ODT, mini tablets
6-12y	<25	Children(school)	Chewable tablets, ODT	Chewable tablets, ODT, mini tabs
12-18y	>25	Adolescent	Small tablets, capsules	Small tablets, capsules, mini tabs
>18y	>40	Adult	Tablets, capsules	Tablet, capsules, mini tabs

Patient Challenges: Raltegravir

Dosing Options--

Tablet, chewable tablet, scored chewable tablet, powder for suspension

Dosing Flexibility PN1066 J Clin Pharmacol 55(7) (2015) 748-756

Age	Cohort	Formulation and Recommended Dose
12-18y	I	400mg FCT 2x day
6-<12y (>25kg)	IIA	400mg FCT 2x day
6-<12y	IIB	~6mg/kg chewable tablet (max 300 mg 2x day)
2-<6y	III	~6mg/kg chewable tablet (max 300 mg 2x day)
6 mths-<2y	IV	~6mg/kg granule for suspension 2x day
4 wks-<6 mths	V	~6mg/kg granules for suspension 2x day

Patient Challenges: Raltegravir and Neonates

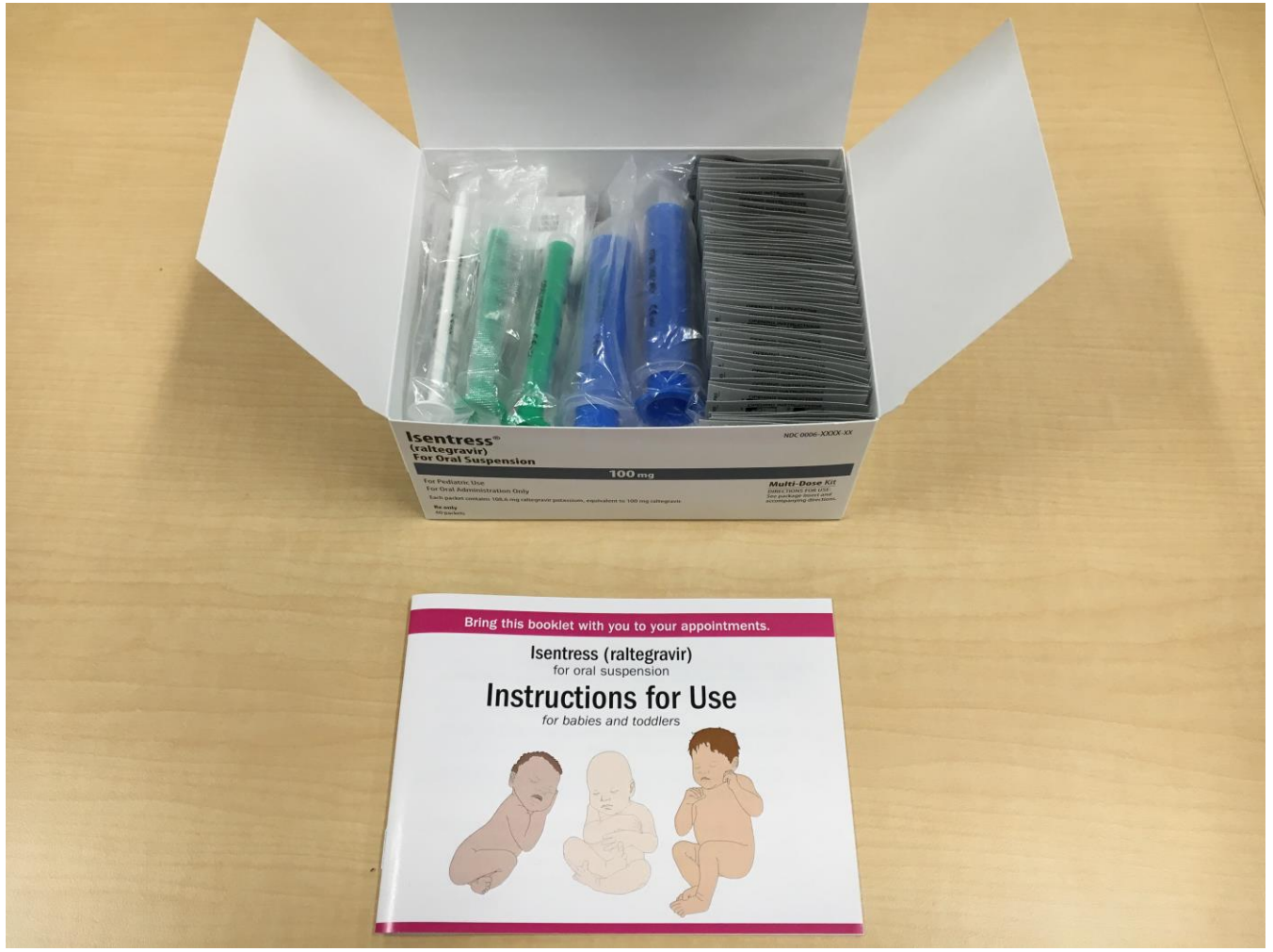
ORAL SUSPENSION:
Full-term neonates (birth to 4 weeks [28 days] of age):

Birth to 1 week:
-Weight 2 to less than 3 kg: 4 mg orally once a day
-Weight 3 to less than 4 kg: 5 mg orally once a day
-Weight 4 to less than 5 kg: 7 mg orally once a day

1 to 4 weeks:
-Weight 2 to less than 3 kg: 8 mg orally twice a day
-Weight 3 to less than 4 kg: 10 mg orally twice a day
-Weight 4 to less than 5 kg: 15 mg orally twice a day

Raltegravir Powder for Suspension

ISENTRESS®
raltegravir



Combination product development the development of a booklet for instructions for use, color coded syringes to add in product constitution and administration. Instructions to aid in accurate syringe dosing.

Dosage Form--Usability Challenges
Oral syringe administration

Clinically proven, patented and designed specifically for children's medicine, CertaDose™ incorporates an easy-to-use, color-coded measurement confirmation onto the syringe for pediatric medications. For more information on keeping children safe from dosing errors, visit http://www.certadose.com

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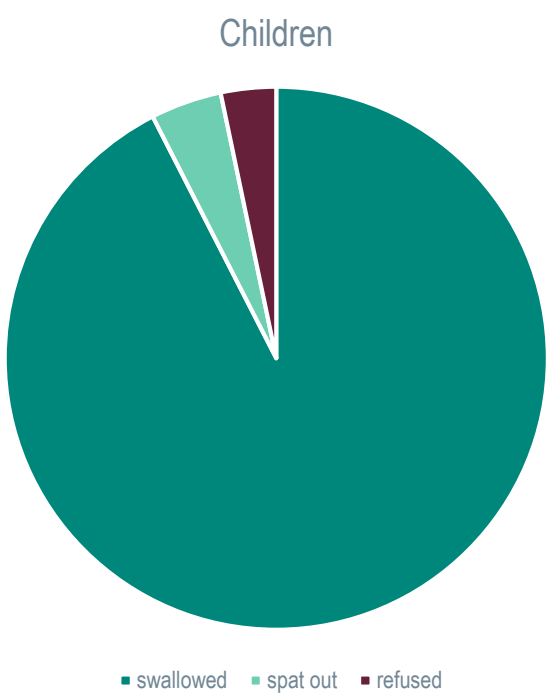
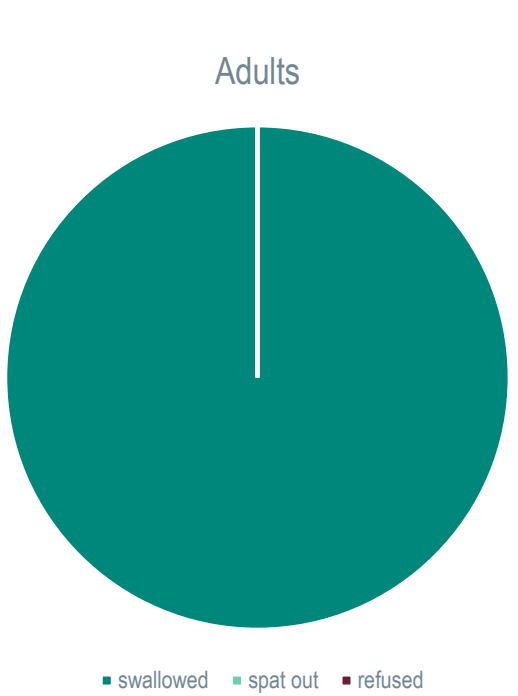
Manufacturing--Excipient Challenges

- Taste masking alternatives
  - alternative sweeteners
    - monk fruit approval EFSA pending
    - stevia approved EFSA
  - Bitter blocker technology of Senomyx now part of Firmenich
- Partnership with vendors and regulatory groups to advance these new approaches to pediatric medicines
- FDA Inactive ingredients list does not highlight those excipients that are used in pediatrics
  - Limited data for excipients alone versus within the context of a formulation

Dosage form—Acceptability Challenges

Evaluation criteria	Children (n = 71, 213 evaluations)	Adults (n = 61, 183 evaluations)
Success in swallowing the formulation		

Acceptability of placebo multiparticulate formulations in children and adults
Felipe L. Lopez, Punam Mistry, Hannah K. Batchelor, Joanne Bennett, Alastair Coupe, Terry B. Ernest, Mine Orlu & Catherine Tuleu
Scientific Reports 8, Article number: 9210 (2018)

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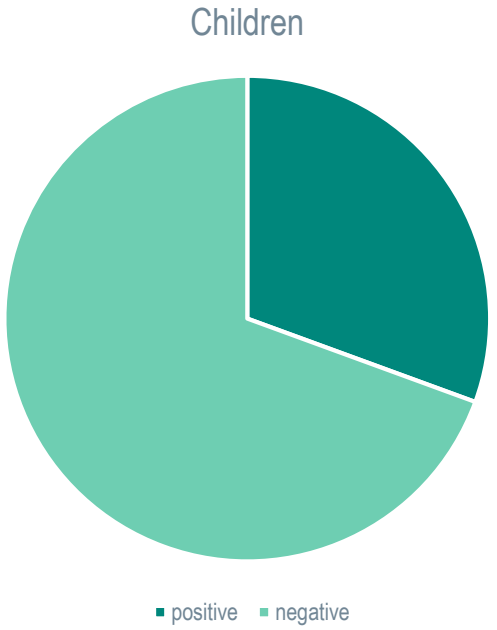
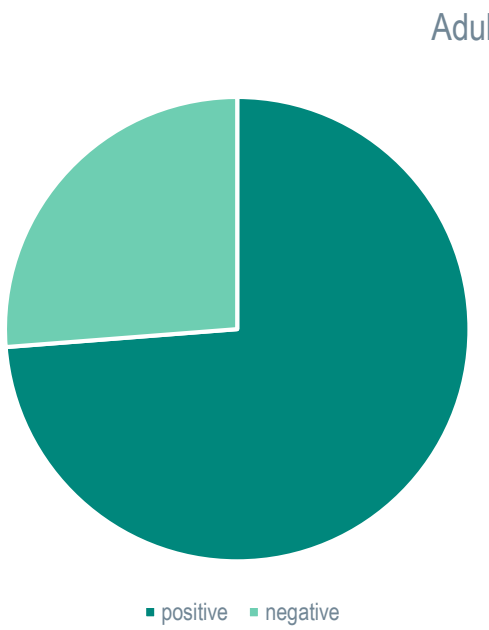
Dosage form—Acceptability Challenges

Evaluation criteria	Children (n = 71, 213 evaluations)	Adults (n = 61, 183 evaluations)
Willingness to take the sample everyday		

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Pediatric Formulation Development: Challenges of Today and Strategies of Tomorrow

More than ever pediatric formulation development is entering a new phase of regulatory requirements for acceptability, reduction of dosing errors and usability. An expansion of tools to assist in administration and to enhance patient adherence. An evolution tools to strengthen PK/PD modeling to inform dosing flexibility requirements. Increasing development and partnership with caregivers for children to better inform and guide formulation development.

Challenge what you think you know—look at mini tablet dosing

Involve patients and their caregivers, clinicians and regulators

A change is going to come...Sam Cooke

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THANK YOU

The future is coming

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