# Regulatory Considerations on Dose Selection for Pediatric Patients

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**Pediatric Inflammatory Bowel Disease Workshop**

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# Outline

- Currently approved treatments for inflammatory bowel disease (IBD)
- Pharmacological targets for IBD in drug development
- Pediatric extrapolation algorithm
- Study design and dose selection approaches used by the approved products for pediatric IBD
- Conclusion

# Approved Small Molecules for IBD

| Small molecule | Class | Crohn's disease | | Ulcerative colitis | |
|---|---|---|---|---|---|
| | | Adults | Peds | Adults | Peds |
| Mesalamine | 5-ASA | - | - | I/M | I (≥ 5 years) |
| Sulfasalazine | 5-ASA | - | - | I/M | I/M (≥ 6 years) |
| Olsalazine | 5-ASA | - | - | M | - |
| Balsalazide | 5-ASA | - | - | I | I (≥ 5 years) |
| Tofacitinib | JAK Inhibitor | - | - | I/M | - |
| Budesonide | corticosteroid | I/M | I (≥ 8 years) | I | - |
| *Prednisone** | corticosteroid | *Yes* | *Yes* | *Yes* | *Yes* |
| *Prednisolone** | corticosteroid | *Yes* | *Yes* | *Yes* | *Yes* |
| *Methylprednisolone** | corticosteroid | - | - | *Yes* | - |

Most of small molecules are approved for mild-to-moderate CD or UC (except for Tofacitinib)

I-Induction of remission M: Maintenance of remission

5-ASA: 5-Aminosalicylates JAK: Janus Kinase

# Approved Biologics for IBD

| Biologic | Class | Crohn's disease | | Ulcerative colitis | |
|---|---|---|---|---|---|
| | | Adults | Peds | Adults | Peds |
| Infliximab | TNF blocker | I/M | I/M (≥ 6 years) | I/M | I/M (≥ 6 years) |
| Adalimumab | TNF blocker | I/M | I/M (≥ 6 years) | I/M | - |
| Certolizumab | TNF blocker | I/M | - | - | - |
| Golimumab | TNF blocker | - | - | I/M | - |
| Vedolizumab | Anti-integrin Agent | I/M | - | I/M | - |
| Natalizumab | Anti-integrin Agent | I/M | - | - | - |
| Ustekinumab | IL-12/23 antagonist | I/M | - | - | - |

All approved biologics were for moderate-severe CD or UC

I-Induction of remission M: Maintenance of remission

# Current Targets for Small Molecules in IBD Drug Development

| New targets | Target | Disease | Status of adult program |
|---|---|---|---|
| Ozanimod (RPC1063) | S1P agonist | CD<br>UC | Ongoing Phase 3<br>Ongoing Phase 3 |
| Amiselimod (MT-1303) | S1P agonist | CD | Completed Phase 2 |
| Filgotinib (GLPG0634) | JAK inhibitor | CD<br>UC | Ongoing Phase 3<br>Ongoing Phase2b/3 |
| Tofacitinib (CP-690,550) | JAK inhibitor | CD<br>UC | Completed Phase 2<br>Approved |
| Upadacitinib (ABT-494) | JAK inhibitor | CD<br>UC | Ongoing Phase 3<br>Ongoing Phase 3 |

S1P: sphingosine 1-phosphate (S1P) receptor agonist
JAK1: Janus Kinase

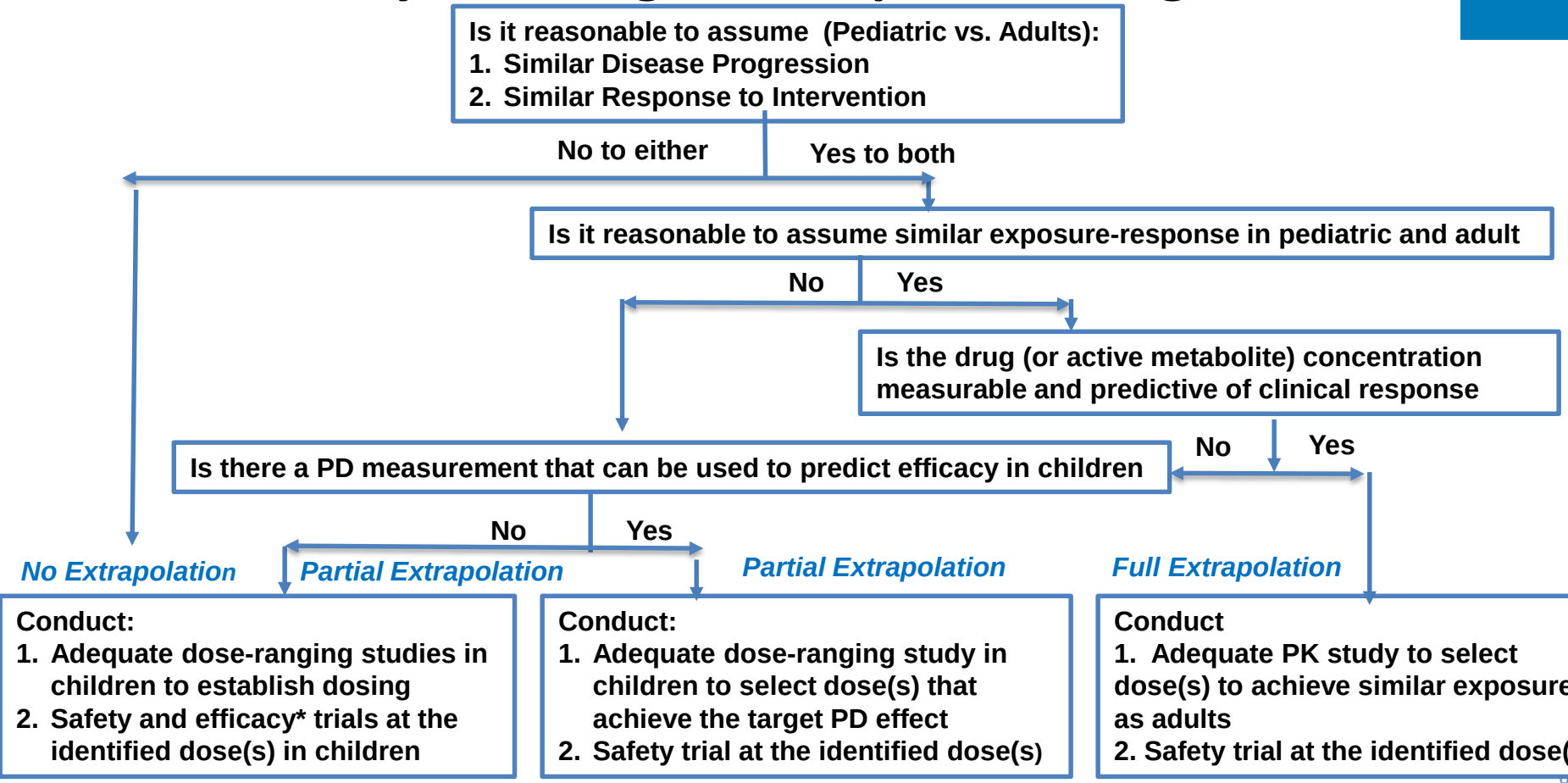
Source: Clinicaltrials.gov (accessed on 13th November 2018)

# Current Targets for Biologics in IBD Drug Development

| New targets | Target | Disease | Status of adult program |
|---|---|---|---|
| Ustekinumab | IL-12/23p40 | CD<br>UC | Approved<br>Ongoing (Phase 3) |
| Risankizumab | IL-23p19 | CD<br>UC | Ongoing (Phase 3)<br>Ongoing (Phase 3) |
| Mirikizumab | IL-23p19 | CD<br>UC | Ongoing (Phase 2)<br>Ongoing (Phase 3) |
| Guselkumab | IL-23p19 | CD<br>UC | Ongoing (Phase 3)<br>Ongoing (Phase 2) |
| Etrolizumab | Anti-integrin | CD<br>UC | Ongoing (Phase 3)<br>Ongoing (Phase 3) |
| SHP647 | anti-MAdCAM | CD<br>UC | Ongoing (Phase 3)<br>Ongoing (Phase 3) |
| ABBV-323 | CD40 antagonist | UC | Ongoing (Phase 2) |
| Eldelumab | anti-CXCL10 | UC | Ongoing (Phase 2) |

Clinicaltrials.gov (accessed on 7th November 2018)

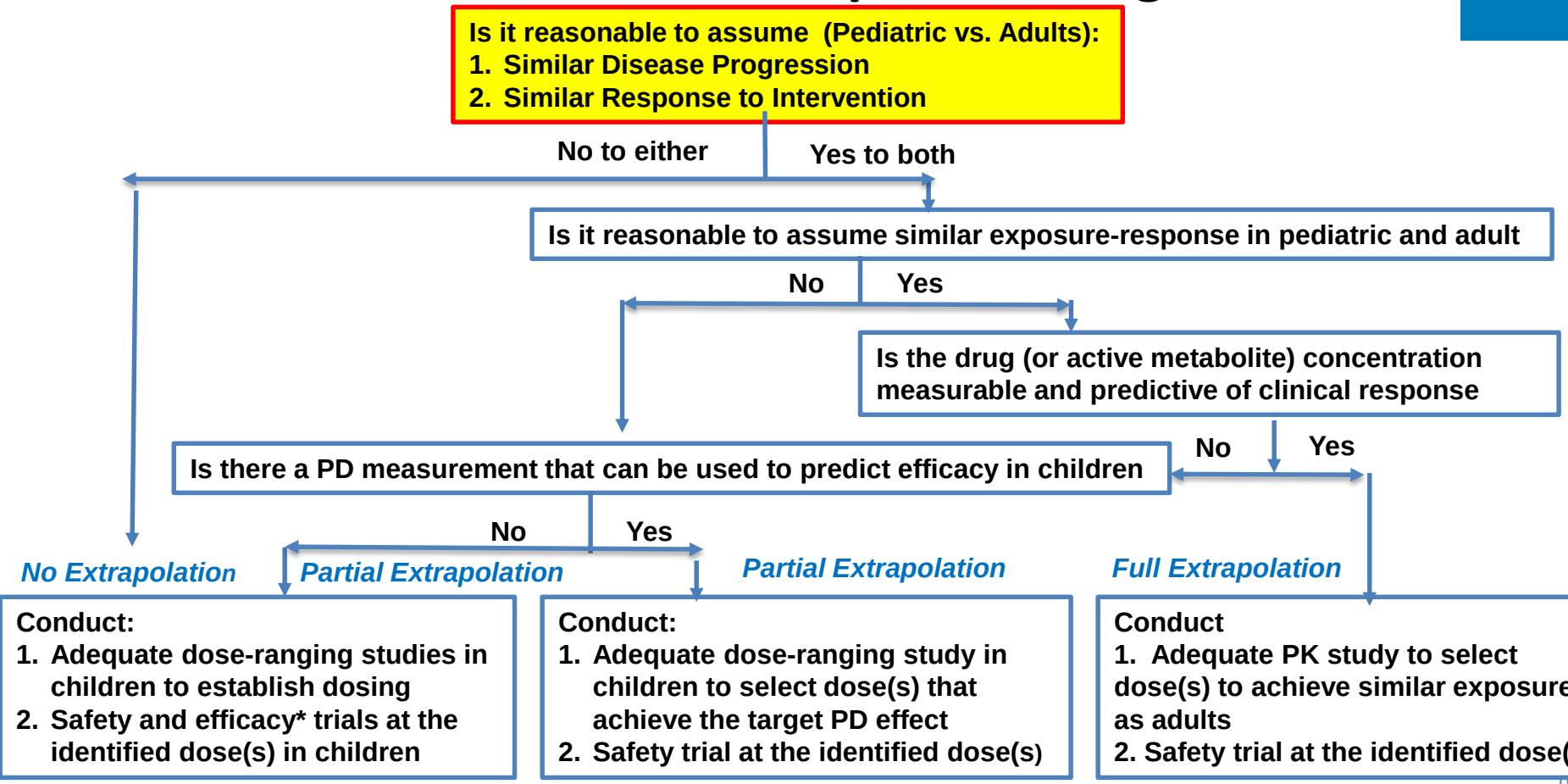
# Pediatric Study Planning & Extrapolation Algorithm




Source: Guidance for Industry: General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products Guidance for Industry , December 2014

* Partial extrapolation, one efficacy trial may be sufficient.

# Where is IBD in Pediatric Extrapolation Algorithm

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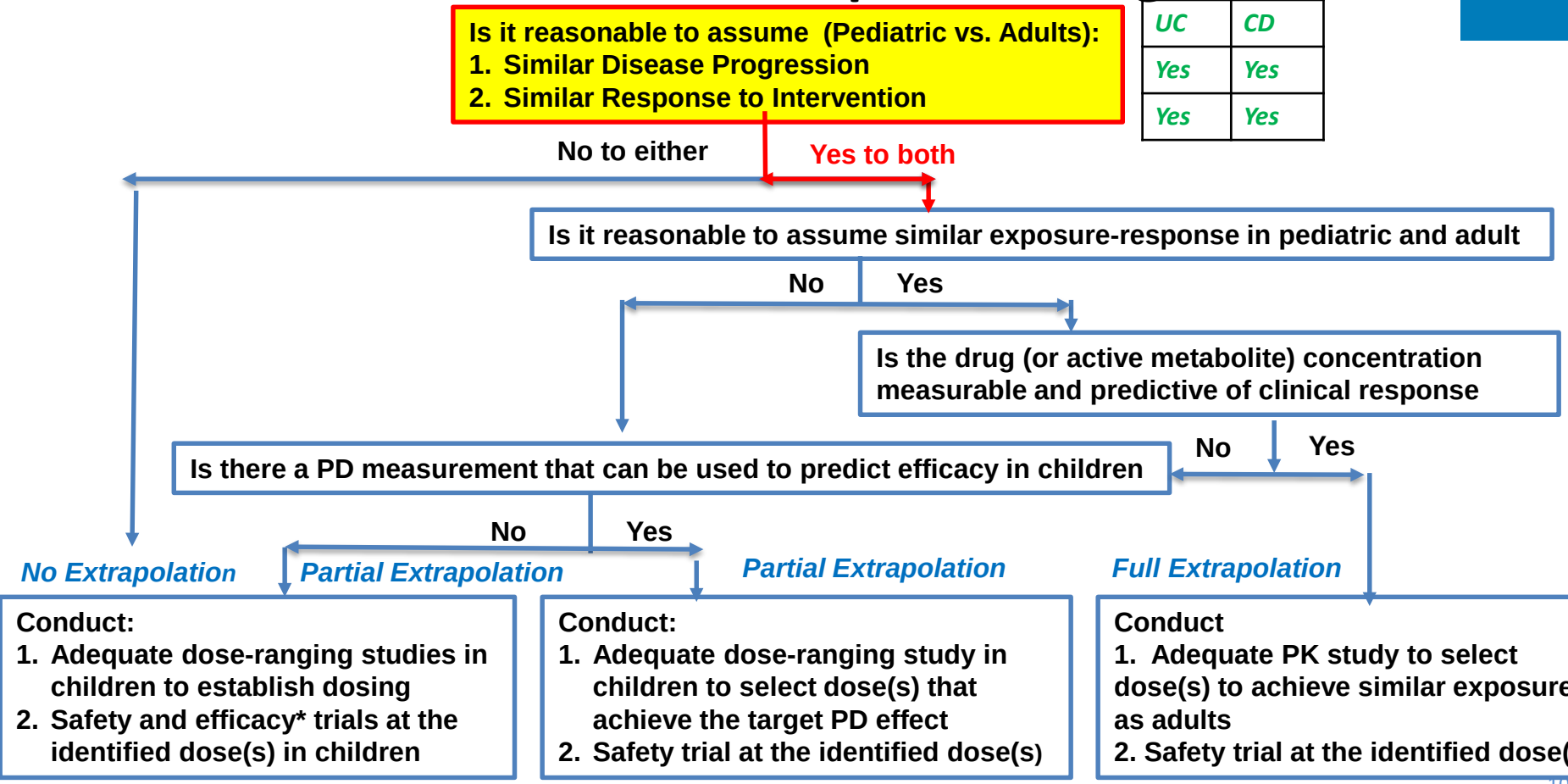


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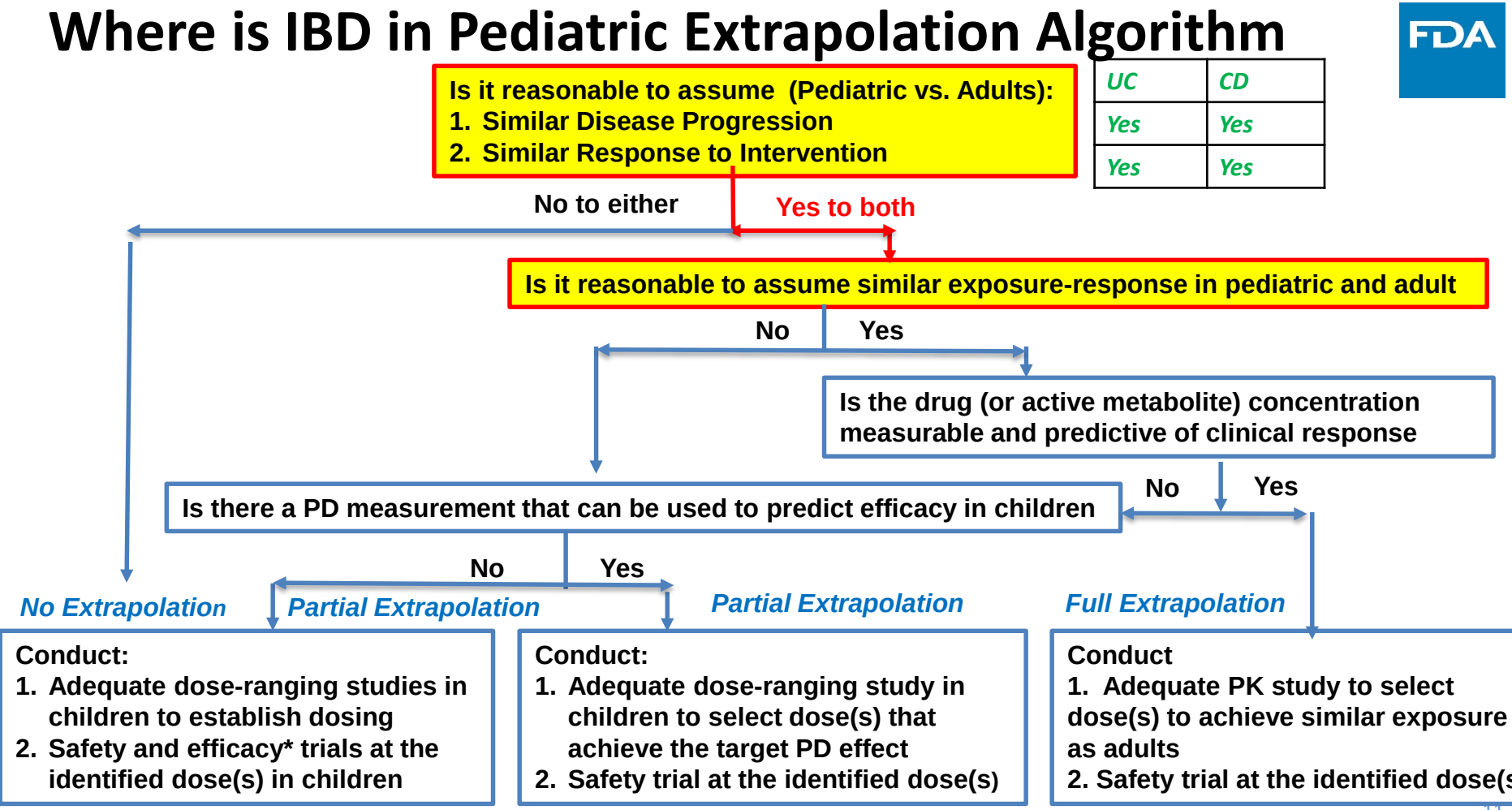


| UC | CD |
|---|---|
| Yes | Yes |
| Yes | Yes |

Source: Guidance for Industry: General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products Guidance for Industry , December 2014

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# Exposure-Response Exploration in Adults and Pediatric Patients with IBD

| Name of Drug | Adult Program | | Pediatric Program | | Similar E-R (Adult vs. Peds) |
|---|---|---|---|---|---|
| | D-R | E-R | D-R | E-R | |
| Budesonide | D-R observed<br>3 dose levels | Not established | No<br>1 dose level | Not established | Unknown |
| Balsalazide | Clear D-R<br>2 dose levels | Not established | slight D-R<br>2 dose levels | Not established | Unknown |
| Mesalamine | D-R observed<br>3 dose levels | Lack of E-R | Lack of D-R<br>2 dose levels | Lack of E-R | Unknown |
| Infliximab (UC induction) | Flat D-R<br>2 dose levels | Yes | No<br>1 dose level | Yes | Similar E-R for induction based on single dose |
| Adalimumab | No<br>1 dose level | Not established | No<br>1 dose level | Not established | Not established |

Similarity in E-R relationship is dependent on disease (CD vs. UC) & drug's mechanism of action

# Where is IBD in Pediatric Extrapolation Algorithm

| UC | CD |
|---|---|
| Yes | Yes |
| Yes | Yes |

**Is it reasonable to assume (Pediatric vs. Adults):**
1. **Similar Disease Progression**
2. **Similar Response to Intervention**

**No to either** — **Yes to both**

**Is it reasonable to assume similar exposure-response in pediatric and adult**

*Not well established for UC &CD*

**No** — **Yes**

**Is the drug (or active metabolite) concentration measurable and predictive of clinical response**

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

**No** — **Yes**

**No** — **Yes**

***No Extrapolation***

**Conduct:**
1. **Adequate dose-ranging studies in children to establish dosing**
2. **Safety and efficacy* trials at the identified dose(s) in children**

***Partial Extrapolation***

**Conduct:**
1. **Adequate dose-ranging study in children to select dose(s) that achieve the target PD effect**
2. **Safety trial at the identified dose(s)**

***Partial Extrapolation***

***Full Extrapolation***

**Conduct**
1. **Adequate PK study to select dose(s) to achieve similar exposure as adults**
2. **Safety trial at the identified dose(s)**

Source: Guidance for Industry: General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products Guidance for Industry , December 2014

* Partial extrapolation, one efficacy trial may be sufficient.

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# Common PD/Biomarkers Evaluated in IBD

| Biomarker | Specificity | Utility |
|---|---|---|
| Serum CRP | Marker for acute Inflammation<br>Not specific to IBD | • Adjunctive use in diagnosis of IBD<br>• Monitoring disease activity<br>• Unspecific for CD vs UC |
| Fecal Calprotectin | Specific marker for Intestinal inflammation | • Adjunctive use in diagnosis of IBD<br>• Monitoring disease activity<br>• Unspecific for CD vs UC |
| Fecal Lactoferrin | Specific marker for Intestinal inflammation | • Adjunctive use in diagnosis of IBD<br>• Monitoring disease activity<br>• Unspecific for CD vs UC |

- No clearly established correlation between biomarkers/PD with IBD clinical efficacy endpoints to predict the efficacy in pediatric


1. Tue Bennike et al "Biomarkers in inflammatory bowel diseases: Current status and proteomics identification strategies", *World J Gastroenterol* 2014 March 28; 20(12): 3231-3244
2. Edward L. Barnes et al "New Biomarkers for Diagnosing Inflammatory Bowel Disease and Assessing Treatment Outcomes", Inflamm Bowel Dis. 2016 December ; 22(12): 2956–2965


CRP: C-reaction Protein

# Where is IBD in Pediatric Extrapolation Algorithm

| UC | CD |
|---|---|
| Yes | Yes |
| Yes | Yes |

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2. **Similar Response to Intervention**

**No to either** / **Yes to both**

**Is it reasonable to assume similar exposure-response in pediatric and adult**

*Not well established for UC &CD*

**No** / **Yes**

**Is the drug (or active metabolite) concentration measurable and predictive of clinical response**

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

**No** / **Yes**

*Unknown for UC &CD*

**No** / **Yes**

***No Extrapolation***

**Conduct:**
1. **Adequate dose-ranging studies in children to establish dosing**
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***Partial Extrapolation***

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**Is it reasonable to assume (Pediatric vs. Adults):**
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**No** / **Yes**

*Unknown for UC &CD*

**No** / **Yes**

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# Pediatric Study Design for Approved IBD Drugs

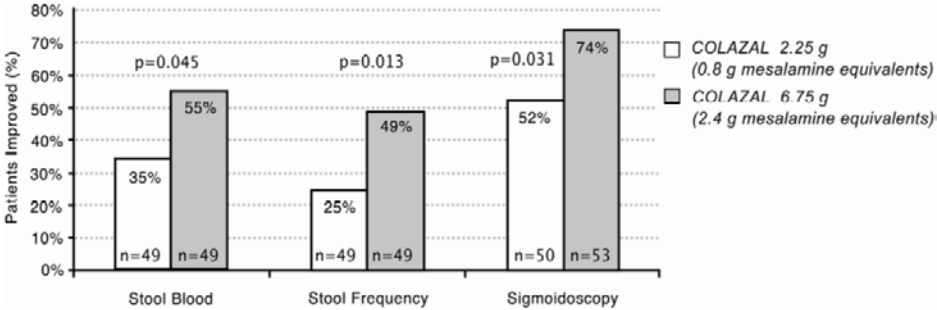
| Name of Drug | Indication | Age group | # of Trials, design | # of Dose levels | # patients | Endpoints |
|---|---|---|---|---|---|---|
| Budesonide | CD | 8 – 17 years | A single trial RD, DB, active control | 1 dose level compared to prednisolone | 46 | Efficacy, safety |
| Balsalazide | UC | 5 - 17 years | A single trial | 2 dose levels | 68 | Efficacy, safety |
| Mesalamine | UC | 5 -17 years | A single trial R, DB, PG | 2 dose levels | 82 | Efficacy, safety |
| Infliximab | UC & CD | 6 -17 years | A separate single trial R, OL for CD & UC | 1 dose level for CD & UC | CD: 112 UC: 60 | Efficacy, safety |
| Adalimumab | CD | 6 - 17 years | A single R, DB | 2 dose levels | 192 | Efficacy, safety |

Source: https://www.accessdata.fda.gov/scripts/cder/daf/

# Pediatric Dose Selection for Balsalazide

- Adult Dose:
  - Evaluated : 2.25 g/day & 6.75 g/day
  - Approved: 6.75 g/day
- Pediatric dose (≥ 5 years):
  - Evaluated

**Figure 1: Percentage of Patients Improved at 8 weeks**




| Dose | Clinical Improvement (Primary Endpoint) | Rectal Bleeding Improvement | Colonic Mucosal Improvement |
|---|---|---|---|
| 2.25 g/day (n=33) | 37% | 54% | 46% |
| 6.75 g/day (n=35) | 45% | 64% | 61% |

  - Approved: Both 2.25 g/day & 6.75 g/day

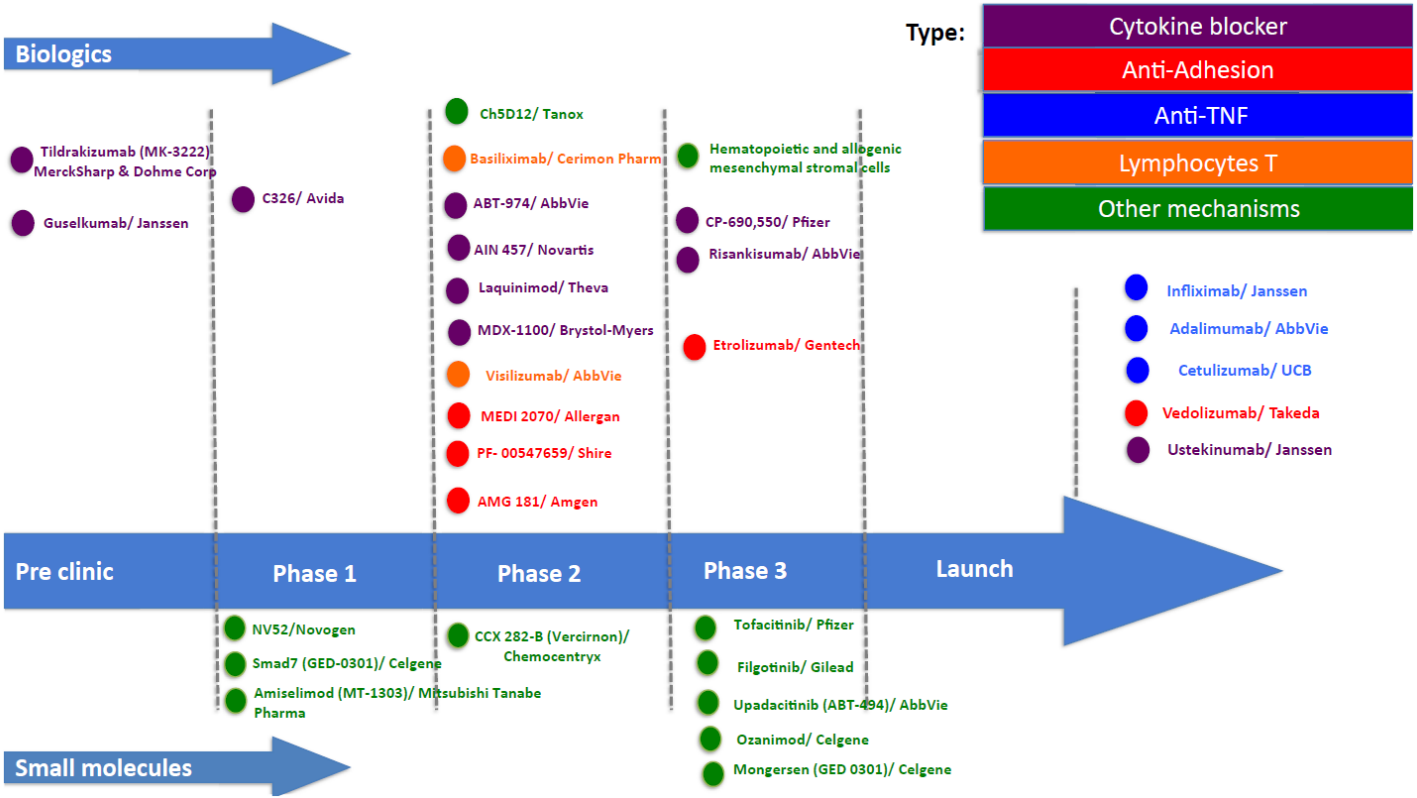
Source: Prescribing Information for Colazal (balsalazide) capsules

# Conclusion

- Disease progression and response to intervention for UC & CD are similar between pediatric and adults
- Limited experience on similarity of E-R relationship between pediatric and adult
- Lack of reliable PD marker that is predictive of efficacy
- Partial extrapolation approach with efficacy assessment in pediatric population is recommended.

# Back-Up

# Current Therapeutic Target in IBD




M. Argollo et al. / Journal of Autoimmunity 85 (2017) 103e116

# Pediatric Dose Selection for Mesalamine

| Adult Approved Dose: 2.4 g/day | | | | | |
|---|---|---|---|---|---|
| | Study 1 | | | Study 2 | |
| Adult Dose | Placebo (n=52) | 1.6 g/day (n=53) | 2.4 g/day (n= 53) | Placebo (n=38) | 4.8 g/day (n=39) |
| Sigmoidoscopic improvement | 27% | No effect | 49% | 26% | 74% |

| Pediatric Evaluated Weight Based Dosing | | | |
|---|---|---|---|
| Weight | 17-33 kg | 33-54 kg | 54-90 kg |
| Low Dose | 1.2 g/day | 2 g/day | 2.4 g/day |
| High Dose | 2 g/day | 3.6 g/day | 4.8 g/day |

| Pediatric Approved Dose: Low Dose | | | | |
|---|---|---|---|---|
| Dose | Success based on TM-Mayo | Complete Response | Success based on PUCAI | Complete Response |
| Low Dose (n=41) | 73% | 34% | 56% | 46% |
| High Dose (n=41) | 70% | 43% | 55% | 43% |

TM-Mayo: Truncated Mayo score, based on the stool frequency and rectal leeding subscales of the Mayo Score

Source: Prescribing Information for Asacol (mesalamine) delayed-released tablet and Delzicol (mesalamine) delayed-release capsules

# Pediatric Dose Selection for Mesalamine

- Evaluated adult doses:1.6g/day, 2.4g/day, 4.8 g/day
- Approved adult dose: 2.4 g/day
- Evaluated pediatric dose:

| Weight | 17-33 kg | 33-54 kg | 54-90 kg | Success based on TM-Mayo | Complete Response | Success based on PUCAI | Complete Response |
|---|---|---|---|---|---|---|---|
| Low Dose (n=41) | 1.2 g/day | 2 g/day | 2.4 g/day | 73% | 34% | 56% | 46% |
| High Dose (n=41) | 2 g/day | 3.6 g/day | 4.8 g/day | 70% | 43% | 55% | 43% |

- Recommended pediatric dose: Low dose
  - Rationale: high dose was not more effective than the low dose

# Approved Products for Pediatric IBD

| Drug | Pharmacological Class | Indication | Induction | Maintenance | Age Range | Route of Administration | Dosing approach |
|---|---|---|---|---|---|---|---|
| Entocort EC budesonide | corticosteroid | Crohn's Mild/moderate | Yes | No | ≥ 8 years | Oral Capsule | 9 mg QD up to 8 weeks, followed by 6 mg QD for 2 weeks |
| Asacol Mesalamine | aminosalicylate | UC mild/moderate | Yes | No | ≥ 5 years | Oral DR tablets | BW based dosing 1.2-2.4 g/day |
| Delzicol Mesalamine | aminosalicylate | UC, Mild/moderate | Yes | No | ≥ 5 years | Oral DR capsule | BW based dosing 1.2-2.4 g/day |
| Colazal balsalazide | aminosalicylate | UC, Mild/moderate | Yes | No | ≥ 5 years | Oral Capsule | 2.25 g/day or 6.75 g/day |
| Prednisone | corticosteroids | UC, Crohn | unknown | unknown | unknown | Oral tablet | |
| Prednisolone | corticosteroids | UC, Crohn | unknow | unknown | unknown | | |
| Infliximab | TNF blocker | UC, moderate/Severe | Yes | Yes | ≥ 6 years | IV infusion | 5 mg/kg |
| | | Crohn moderate/Severe | Yes | Yes | ≥ 6 years | IV infusion | 5 mg/kg |
| adalimumab | TNF blocker | Crohn moderate/Severe | Yes | Yes | ≥ 6 years | SC | BW based dosing 40 mg -160 mg |

# Dose-Selection Approaches Used for Small Molecules Approved for Pediatric IBD

| | Evaluated Adult Doses | Approved Adult dose | Evaluated Pediatric doses | Approved Pediatric Dose |
|---|---|---|---|---|
| Budesonide | 1.5 mg BID,<br>4.5 mg BID,<br>7.5 mg BID<br>9 mg QD<br>4.5 mg BID | 9 mg QD | 9 mg QD for 8 wks, 6 mg QD for 4 wks | 9 mg/6 mg |
| Balsalazide | 2.25 g/day or<br>6.75 g/day | 6.75 g/day | 2.25 g/day & 6.75 g/day | 2.25 g/day &<br>6.75 g/day |
| Mesalamine | 1.6g/day,<br>2.4g/day,<br>4.8 g/day | 2.4 g/day | <table><tr><td>Weight (kg)</td><td>17-33</td><td>33-54</td><td>54-90</td></tr><tr><td>Low Dose (g/day)</td><td>1.2</td><td>2</td><td>2.4</td></tr><tr><td>High Dose (g/day)</td><td>2</td><td>3.6</td><td>4.8</td></tr></table> | WT based<br>Low Dose |

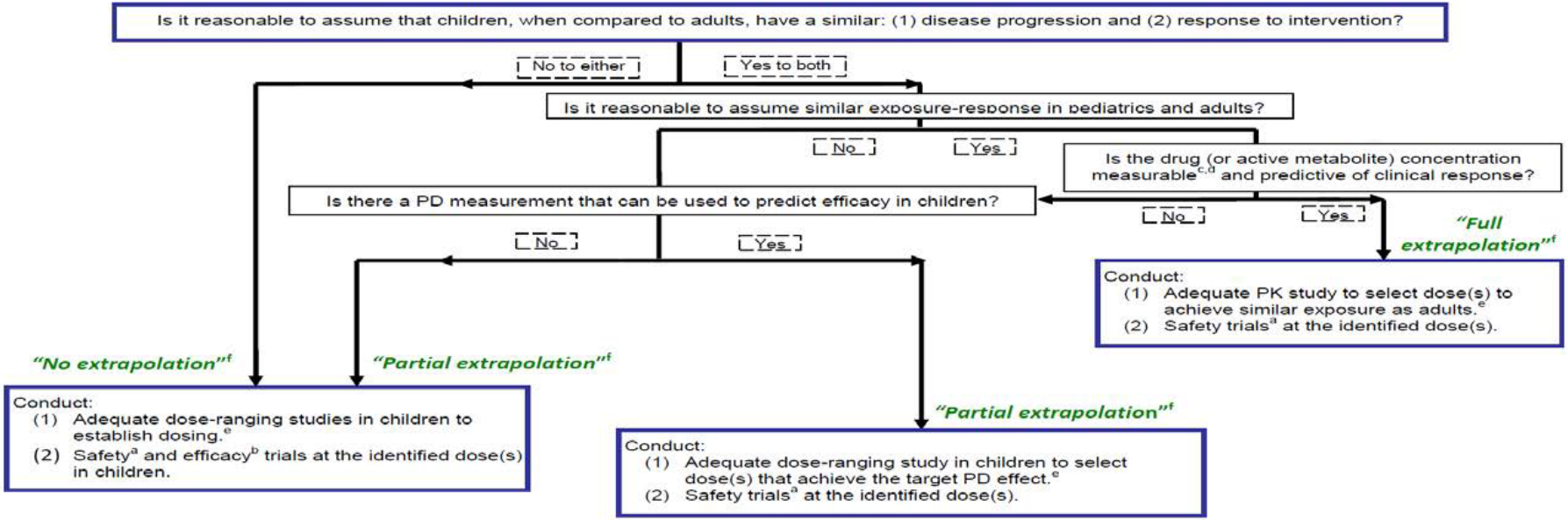
https://www.accessdata.fda.gov/scripts/cder/daf/

# Study Design of Pediatric IBD

| Name of Drug | Indication | Adult study Design | | | | Pediatric Study Design | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Dose-ranging | Number of dose | Established E-R or D-R | Approved dose | Phase 2 /phase 3 | Number of dose levels | # patients | Endpoints | D-R<br><br>E-R | Approved Dose |
| budesonide | CD | 1.5 BID,<br>4.5 BID,<br>7.5 BID<br><br>9 mg QD | 3 | D-R<br><br>No E-R established | 9 mg | A single trial | 1 dose level (9 mg) compared to prednisolone | 46 | Efficacy, safety | No D-R<br>No E-R<br><br>PK in separate PK small study | Single dose |
| balsalazide | UC | 2.25 g/day or<br>6.75 g/day | 2 | Clear D-R<br><br>No E-R explored | 6.75 | A single trial | 2 dose levels 2.25 g/day or 6.75 g/day | 68 | PK, Efficacy, safety | slight D-R<br><br>No E-R explored | Both doses |
| Mesalamine | UC | 2 trials<br><br>1.6g/day,<br>2.4g/day,<br>4.8 g/day | 3 dose levels | D-R | 2.4 g/day | A single trial R, DB, PG | 2 dose levels | 82 | Efficacy, safety | Flat dose-response<br><br>No E-R | Low dose group |
| Infliximab | UC & CD | 5 mg/kg<br>10 mg/kg | 2 | No D-R<br>E-R | 5 mg/kg | R, OL | 1 dose level for CD (5mg/kg) | CD: 112<br>UC: 60 | Efficacy, safety | E-R | Similar E-R Adult vs. ped |
| adalimumab | CD | | | | | A single R, DB | 2 dose levels | 192 | Efficacy, safety | slight D-R<br><br>No E-R | Weight based |

Adalimumab: Concentrations and response rates at week 26 were comparable between adults and children

# Pediatric Study Planning & Extrapolation Algorithm




Footnotes:

a. For locally active drugs, includes plasma PK at the identified dose(s) as part of safety assessment.
b. For partial extrapolation, one efficacy trial may be sufficient.
c. For drugs that are systemically active, the relevant measure is systemic concentration.
d. For drugs that are locally active (e.g., intra-luminal or mucosal site of action), the relevant measure is systemic concentration only if it can be reasonably assumed that systemic concentrations are a reflection of the concentrations at the relevant biospace (e.g., skin, intestinal mucosa, nasal passages, lung).
e. When appropriate, use of modeling and simulation for dose selection (supplemented by pediatric clinical data when necessary) and/or trial simulation is recommended.
f. For a discussion of no, partial and full extrapolation, see Dunne J, Rodriguez WJ, Murphy MD, et al. "Extrapolation of adult data and other data in pediatric drug-development programs." Pediatrics. 2011 Nov;128(5):e1242-9.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