Pediatric Inflammatory Bowel Disease: Developing Drugs for Treatment

Guidance for Industry

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

July 2024
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TABLE OF CONTENTS

Pediatric Inflammatory Bowel Disease: Developing Drugs for Treatment Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

The purpose of this guidance is to help sponsors in the clinical development of drugs to treat pediatric patients with inflammatory bowel disease (IBD).[2] Specifically, this guidance provides the Food and Drug Administration's (FDA's) recommendations about the necessary attributes of clinical studies for drugs being developed for the treatment of pediatric ulcerative colitis (UC) or pediatric Crohn's disease (CD), including study population, study design, efficacy considerations, and safety assessments.[3]

This guidance does not address extraintestinal manifestations, stricturing or fistulizing disease, or the treatment or prevention of long-term complications of pediatric UC or CD. Additionally, this guidance is not intended to address the treatment of monogenic IBD or IBD unclassified. The recommendations for clinical study design in this guidance are based upon the assumption that a robust development program is being conducted in adults and that efficacy data from adults will be available to help inform the pediatric program and to support extrapolation of efficacy.

Sponsors seeking to develop a drug only for pediatric UC or CD patients in the absence of an adult program should meet with the appropriate review division to discuss their proposals.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of

[1] This guidance has been prepared by the Division of Gastroenterology (the Division) in the Center for Drug Evaluation and Research at the Food and Drug Administration.

[2] For the purposes of this guidance, all references to *drugs* include both human drugs and therapeutic biological products unless otherwise specified.

[3] In addition to consulting guidances, sponsors are encouraged to contact the Division to discuss specific issues that arise during the development of drugs to treat pediatric UC or CD.

the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Pediatric IBD is a chronic, immune-mediated disorder characterized by relapsing and remitting intestinal inflammation. Pediatric UC is a type of pediatric IBD that is predominantly restricted to the mucosa of the large intestine. Clinical signs and symptoms of pediatric UC include diarrhea, hematochezia, abdominal pain, and fecal urgency (Ungaro et al. 2017). Pediatric CD is a type of pediatric IBD characterized by transmural inflammation that may affect any segment(s) of the gastrointestinal tract from the mouth to the anus and may be associated with fibrosis, strictures, and perforations. Clinical signs and symptoms of pediatric CD include abdominal pain, diarrhea, fatigue, weight loss, growth impairment, and perianal disease (Torres et al. 2017). In addition, potential extraintestinal manifestations of pediatric IBD include decreased bone mass, peripheral arthritis, aphthous stomatitis, uveitis, pyoderma gangrenosum, erythema nodosum, psoriasis, and primary sclerosing cholangitis (Greuter et al. 2017).

The treatment goals for pediatric UC or CD include resolution or reduction of the signs and symptoms of active disease to provide relief to the patient and healing or control of the underlying inflammation and its complications.

In general, the pathophysiology, disease characteristics, and response to treatment of UC or CD are sufficiently similar between adult and pediatric patients to support extrapolation of efficacy from adequate and well-controlled trials in adult subjects for the same indication. Extrapolation of efficacy from one pediatric age group (e.g., adolescents) to another (e.g., 2 years of age to less than 12 years of age) may further be supported depending on the robustness of the available adult and adolescent data. However, the degree to which efficacy can be extrapolated may depend on the pharmacology of the drug and the amount of information available on the molecule and other drugs in the same class in adult and pediatric patients. In general, as a part of the collective evidence (i.e., in addition to extrapolation of efficacy from adult data) to inform the benefit-risk assessment, FDA recommends a clinical study that includes assessments of safety, pharmacokinetics, and efficacy of the drug in pediatric subjects with UC or CD. The pediatric study should be aligned as closely as possible with the adult phase 3 program with respect to the study design, patient population, endpoints, and timing of assessments to facilitate the benefit-risk assessment.

For pediatric UC, the recommended approach is to use the same criteria to define disease activity and endpoints in pediatric subjects as in adult subjects (i.e., the modified Mayo Score (mMS)).[4]

[4] The mMS is a composite score consisting of rectal bleeding, stool frequency, and endoscopy subscores, adapted from the originally published Mayo Score. The previously used physician global assessment component is excluded to reduce subjectivity and focus the evaluation on the subject's directly reported symptoms and directly observable endoscopic findings. See Table 1 in the Appendix.

For pediatric CD, the Pediatric Crohn's Disease Activity Index (PCDAI),[5] an index comprising clinical and laboratory variables that estimate the severity of disease activity in pediatric CD, has been the most commonly used tool in studies intended to support approval of treatments for pediatric CD. However, the PCDAI has been shown to be poorly associated with intestinal inflammation (Turner 2017). Given the limitations of the PCDAI, the recommended approach to define disease activity and endpoints is to incorporate an assessment of underlying inflammation with ileocolonoscopy, in addition to the signs and symptoms of CD using the PCDAI. The same endoscopic criteria should be used to define disease activity and endpoints in pediatric subjects as in adult subjects (i.e., the Simple Endoscopic Score for Crohn's Disease (SES-CD)).[6]

III. DEVELOPMENT PROGRAM

A. Study Population

Sponsors developing drugs for the treatment of pediatric UC or CD should consider the following:

- Sponsors should enroll pediatric subjects 2 to 17 years of age. For subjects diagnosed with IBD younger than 6 years of age (e.g., very early onset IBD), the sponsor should perform a thorough evaluation to exclude monogenic IBD and inherited conditions that may present similarly to IBD before study participation.

- Subjects should have a confirmed diagnosis of pediatric UC or CD based on documented findings on endoscopy and histopathology.

- For drugs intended to treat pediatric UC:

  - For moderately to severely active pediatric UC, subjects should have a score of 5 to 9 on the mMS, including an endoscopy subscore of at least 2.

  - For mildly to moderately active pediatric UC, subjects should have a score of at least 4 on the mMS, including an endoscopy subscore of at least 2 and a rectal bleeding subscore of at least 1.

- For drugs intended to treat pediatric CD:

  - For moderately to severely active pediatric CD, subjects should have a score of at least 30 on the PCDAI and a score of at least 6 (or at least 4 if isolated ileal disease) on the SES-CD.

[5] The PCDAI is a weighted index comprising eight clinical and laboratory variables that estimate disease severity in Crohn's disease. See Table 3 in the Appendix.

[6] The SES-CD is a composite score consisting of ulcer size, amount of ulcerated surface, amount of affected surface, and the presence of narrowing. See Table 4 in the Appendix.

- For mildly to moderately active pediatric CD, sponsors should discuss eligibility criteria with the appropriate review division.

- For drugs intended to treat moderately to severely active pediatric UC or CD:

  - Sponsors should enroll pediatric subjects across the whole range of disease severity categories.

  - When appropriate,[7] sponsors should aim to include a balanced representation of pediatric subjects who have never received treatment with a biological product and pediatric subjects who have previously demonstrated an inadequate response to one or more biological products or other advanced therapies.

- Sponsors should enroll pediatric subjects who reflect the characteristics of clinically relevant populations, including with regard to race and ethnicity, and should consider clinical study sites that include higher proportions of racial and ethnic minorities to recruit a diverse study population.[8]

- We encourage the inclusion of adolescent subjects (subjects 12 to 17 years of age inclusive) in adult CD or UC clinical trials, provided that preliminary safety and efficacy data in adult subjects support enrollment. FDA encourages sponsors to discuss the proposed sample size of adolescent subjects with the appropriate review division at the time of protocol development.

B. Study Design

Sponsors developing drugs for the treatment of pediatric UC or CD should consider the following for study design:

- We recommend a randomized, double-blind study that evaluates at least two dose levels for each age and/or weight cohort, respectively.[9]

[7] The known and anticipated risks of a new drug or drug class may impact whether the drug is appropriate to be studied in pediatric subjects as a first-line therapy or reserved for those who have failed one or more approved therapies.

[8] For additional recommendations, see the guidance for industry *Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs* (November 2020). We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[9] In the setting where the drug is approved for use in adult populations, the risks of randomizing pediatric subjects with active disease (at risk of disease worsening and complications) to placebo may outweigh the potential benefits of study enrollment. Sponsors interested in pursuing an active comparator study should discuss the study design with the appropriate review division.

- For drugs intended to be administered chronically, we recommend a blinded treatment period of at least 52 weeks to assess both early efficacy and durability of response over time and to ensure adequate longer term exposure to characterize safety.

For dose selection, sponsors should consider the following:

- Dose selection for pediatric studies should be guided by a well-characterized dose/exposure-response relationship[10] in adult subjects for the same indication.

- It is often unknown before evaluation in pediatric subjects whether a similar dose(s) or systemic exposure(s) as for adult subjects will achieve comparable efficacy and safety in pediatric subjects. Therefore, we recommend an exploration of a range of doses to help optimize the pediatric dose(s). All selected pediatric doses should be expected to provide a therapeutic benefit.

  - Dose selection should be guided by modeling and simulation using available pharmacokinetic (PK) and pharmacodynamic (PD) data based on well-characterized dose/exposure-response relationship in adult subjects for the same indication. If available, pediatric PK data from other indications may be leveraged to help support the initial dose selection for pediatric subjects with UC or CD.

  - The predicted systemic exposure should be confirmed in the target patient population and across the age groups. A standalone pediatric PK study or a PK lead-in period in a pediatric efficacy study may be utilized to confirm the predicted exposures for the selected dosing regimens across the age groups. FDA encourages sponsors to assess relevant PD data (e.g., clinical remission, endoscopic remission), if available, along with PK data to further guide dose selection.

    - If a sponsor uses a PK lead-in period, the study design should allow for the interim analysis of PK data and for the sponsor to plan for dose adjustment if necessary. The pediatric dosage form used in these studies should be amenable to dose adjustment.

For study sample size, sponsors should consider the following:

- The sample size should be sufficient to ensure collection of data on an adequate number of subjects through week 52 to inform the efficacy and safety of the drug for chronic use in pediatric subjects. In most cases, FDA recommends a sample size of at least 50 to 60 subjects per treatment arm to ensure an adequate number of subjects reach the end of the study to inform the benefit-risk assessment of the dosages studied. FDA encourages sponsors to discuss the proposed sample size with the appropriate review division at the time of protocol development because product-specific considerations and study design may impact the sample size.

[10] For drugs that have limited systemic absorption, FDA encourages sponsors to discuss their dose selections with the appropriate review division.

- The protocol should specify enrollment targets for each age cohort (e.g., 2 to 5 years of age, 6 to 11 years of age, 12 to 17 years of age) to ensure adequate representation across the range of ages and body weights.

C. Efficacy Considerations

1. Efficacy Assessments

For pediatric UC, sponsors should consider the following for efficacy assessments:[11]

- We recommend evaluating the proportion of pediatric subjects achieving clinical remission as the primary endpoint.
  - Clinical remission is defined as an mMS of 0 to 2, including the following three components:
    1) Stool frequency subscore = 0 or 1[12]
    2) Rectal bleeding subscore = 0
    3) Centrally read endoscopy subscore = 0 or 1 (score of 1 modified to exclude friability)[13]
       - Although historically sponsors have used sigmoidoscopy for the endoscopic assessment in UC, we recommend that sponsors use colonoscopy to document disease activity in all involved segments of the colon.
       - To calculate the weekly mMS components (stool frequency and rectal bleeding subscores), we recommend defining a 7-day period during which the daily scores are collected before the specified study visit in which the mMS is calculated. The

[11] We recommend using the same primary and secondary endpoints and timing of assessment in pediatric subjects as in adult subjects to facilitate extrapolation of efficacy from adult trials. See the draft guidance for industry *Ulcerative Colitis: Developing Drugs for Treatment* (April 2022). When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[12] For drugs intended to treat mildly to moderately active pediatric UC, the recommended definition of remission should be modified to include a stool frequency subscore of 0 or 1 and no greater than baseline (start of study).

[13] We recommend using centralized reading of endoscopies as the primary approach to scoring the endoscopic component of the primary and secondary endpoint assessments. Both the endoscopist performing the procedure and the central readers reviewing high-definition video recordings of the procedure should be blinded to treatment assignment and should document the endoscopic findings. The protocol should specify clearly how discrepancies between the findings by the endoscopist and the central reader will be handled in the efficacy analyses (e.g., adjudication by a third reader). Efforts should be made to minimize bias and standardize reading of endoscopy across study sites and among investigators through training and education on the definition of each item described in the scale. Sponsors should draft charters that standardize procedures, video recordings and equipment, and endoscopy assessment early in drug development and share them with the Division for comment.

subscores should be calculated by averaging the daily scores from within this 7-day period, excluding the day of bowel preparation and day of endoscopy. FDA recommends a minimum of 3 consecutive days of completed diary entries or 4 nonconsecutive days; otherwise, the score should be considered *missing*.

- We recommend the following secondary endpoints as defined:

  - **Clinical response:** a decrease from baseline in the mMS of greater than or equal to 2 points and at least a 30 percent reduction from baseline, and a decrease in rectal bleeding subscore of greater than or equal to 1 or an absolute rectal bleeding subscore of 0 or 1.

  - **Corticosteroid-free remission:** pediatric subjects who are in clinical remission (defined by the mMS) at the conclusion of the study (e.g., 52 weeks) and have no corticosteroid exposure during a prespecified period (e.g., at least 8 to 12 weeks) before that assessment.

    - The proportion of subjects achieving corticosteroid-free remission, of those who were using corticosteroids at enrollment, is of interest and should be reported.

  - **Endoscopic improvement:** a centrally read endoscopy subscore of 0 or 1 (score of 1 modified to exclude friability).

  - **Endoscopic remission:** a centrally read endoscopy subscore of 0.

    - We do not recommend the use of the term *mucosal healing* at this time because there is no consensus as to how best to define this concept.

  - **Maintenance of remission.** We recommend the following to demonstrate the durability of benefit:

    - For study designs in which pediatric subjects who achieve clinical response at the end of the induction phase are rerandomized in the maintenance phase, we recommend that sponsors assess the proportion of subjects who maintain clinical remission (defined by the mMS) within the subset of subjects who enter the maintenance phase in clinical remission to support the ability of the therapy to maintain a durable state of clinical remission.

    - For study designs in which pediatric subjects are treated continuously without rerandomization (treat-through design), sponsors should assess the proportion of subjects who individually achieve clinical remission (defined by the mMS) at both early (e.g., 8 weeks) and late (e.g., 52 week) time points to demonstrate that a clinical benefit was attained and was durable.

For pediatric CD, sponsors should consider the following for efficacy assessments:[14]

- We recommend the following coprimary endpoints as defined that evaluate a drug's effect on signs and symptoms *and* on underlying mucosal inflammation:
  - **Clinical remission:** a PCDAI score of 10 or less.
    - To calculate the weekly PCDAI components (abdominal pain, patient functioning, and stools), we recommend defining a 7-day period during which the daily scores are collected before the specified study visit in which the PCDAI is calculated. The scores should be calculated by averaging the daily scores from within this 7-day period, excluding the day of bowel preparation and day of endoscopy. FDA recommends a minimum of 3 consecutive days of completed diary entries or 4 nonconsecutive days; otherwise, the score should be considered missing.
  - **Endoscopic remission:** an SES-CD of 0 to 2. An alternative definition of an SES-CD of 0 to 4, with no individual subscore greater than 1, may also be acceptable.[15]
- We recommend the following secondary endpoints as defined:
  - **Clinical response:**[16] a decrease of at least 15 points on the PCDAI.
  - **Endoscopic response:**[17,18] a greater than 50 percent reduction from baseline on the SES-CD.
  - **Corticosteroid-free remission:** pediatric subjects who are in clinical remission (defined by the PCDAI) at the conclusion of the study (e.g., 52 weeks) and have no corticosteroid exposure during a prespecified period (e.g., at least 8 to 12 weeks) before that assessment.

[14] We recommend using a similar coprimary and secondary endpoint approach in pediatric subjects as in adult subjects consisting of an assessment of the signs and symptoms of CD (i.e., the PCDAI) and underlying inflammation (i.e., SES-CD) to facilitate extrapolation of efficacy from adult trials. See the draft guidance for industry *Crohn's Disease: Developing Drugs for Treatment* (April 2022). When final, this guidance will represent the FDA's current thinking on this topic.

[15] We acknowledge that not all drugs may be able to achieve endoscopic remission within the duration of the clinical study and that there are currently limited data on the ability of available approved drugs to induce endoscopic remission. As a result, it may be acceptable to assess endoscopic response as the endoscopic coprimary endpoint. If endoscopic response is included as one of the two coprimary endpoints, then endoscopic remission should be assessed as a secondary endpoint.

[16] Although clinical or endoscopic response is not the final treatment goal, this definition may also be used as a criterion at the end of induction to rerandomize subjects who are demonstrating improvement to continue into a maintenance phase in the induction or maintenance design.

[17] See footnote 15.

[18] See footnote 16.

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299 were using corticosteroids at enrollment, is of interest and should be reported.
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301 – **Maintenance of remission.** We recommend the following to demonstrate the
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305 end of the induction phase are rerandomized in the maintenance phase, we
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307 remission within the subset of subjects who enter the maintenance phase in
308 clinical remission to support the ability of the therapy to maintain a durable state
309 of remission.
310
311 ▪ For study designs in which pediatric subjects are treated continuously without
312 rerandomization (treat-through design), sponsors should assess the proportion of
313 subjects who individually achieve clinical remission (i.e., defined by PCDAI) at
314 both early (e.g., 8 weeks) and late (e.g., 52 week) time points to demonstrate that
315 a clinical benefit was attained and was durable. Sponsors should perform a similar
316 analysis for the SES-CD.
317
318 – **Composite endpoint of clinical remission and endoscopic remission.**[19] A
319 secondary endpoint should assess the proportion of pediatric subjects who achieved
320 both clinical remission and endoscopic remission. This endpoint should be assessed at
321 the conclusion of the study (e.g., 52 weeks).
322
323 For pediatric UC and CD, we recommend that sponsors consider the following exploratory
324 endpoints:
325
326 • **Interim clinical assessments based on noninvasive measures.** Sponsors should
327 incorporate interim assessments of clinical remission (without endoscopic assessment) at
328 prespecified intermediate time points during the study, up until and including the last
329 study visit (e.g., 52 weeks), to support maintenance of remission.
330
331 • **Histologic response or remission.** At this time, there is no scientific consensus on a
332 definition of, or scoring system for, histologic resolution of mucosal inflammation in
333 subjects who have achieved endoscopic remission in UC or CD. Sponsors should provide
334 adequate justification for the proposed endpoint definitions, grading scales, and scoring
335 techniques.
336
337 *2. Statistical Considerations*
338
339 The efficacy evaluation of a study without a placebo control arm is challenging; therefore, the
340 assessment of the efficacy data to support a proposed indication in pediatric UC or CD will be
341 based on an evaluation of the collective evidence, rather than the results of a single hypothesis

[19] See footnote 15.

test. To support the assessment of efficacy in pediatric subjects, we recommend sponsors include the following prospectively planned comparisons:

- A comparison of the remission rate in pediatric subjects to the remission rate achieved by adult subjects on both active treatment and placebo, estimated from relevant previously conducted clinical studies with the same drug. The planned analysis should incorporate the uncertainty in the estimated responses. This analysis should be conducted for the primary and key secondary endpoints of interest.

- A comparison of the clinical remission rate in pediatric subjects to the clinical remission rate in adult placebo subjects using an estimate based on a prespecified systematic review and meta-analysis of other randomized adult trials with sufficiently similar characteristics to the pediatric study. When possible, sponsors should use subject-level data rather than study-level data, and any analyses of integrated data from multiple studies should be stratified by study.[20]

- A comparison of remission rates between dose levels evaluated in pediatric subjects for the primary and key secondary endpoints of interest.

- An exposure-response analysis for efficacy in pediatric subjects and a comparison of those results with adult exposure-response analysis.

Additionally, for sponsors developing drugs for the treatment of pediatric UC or CD we recommend the following:

- Sponsors should consider Bayesian methods utilizing adult data in the analysis of the pediatric study.

- To gain precision and, for nonrandomized comparisons with external control arms, reduce bias in the evaluation of overall treatment effects (e.g., the overall difference in remission rates), sponsors should adjust statistical analyses for subject characteristics at baseline that may impact efficacy outcomes (e.g., disease severity, concurrent use of corticosteroids, prior biological product use).[21]

- Sponsors should conduct efficacy analyses in all randomized pediatric subjects.

- Sponsors should prespecify methods to handle intermittent missing data.

[20] For further details, see the draft guidance for industry *Meta-Analyses of Randomized Controlled Clinical Trials to Evaluate the Safety of Human Drugs or Biological Products* (November 2018). When final, this guidance will represent the FDA's current thinking on this topic.

[21] See the draft guidance for industry *Adjusting for Covariates in Randomized Clinical Trials for Drugs and Biological Products* (May 2021). When final, this guidance will represent the FDA's current thinking on this topic.

- Sponsors should prespecify a primary estimand of interest for each endpoint and justify that it is meaningful and that it can be estimated with minimal and plausible assumptions with the proposed analysis. The estimand is a precise description of the treatment effect, reflecting the clinical question posed by a given clinical study objective.[22] The following recommendations apply:

  - Sponsors should consider important intercurrent events when defining the estimand, including treatment discontinuation, use of rescue medication, and UC- or CD-related surgery.

  - Sponsors should consider potential strategies for defining and handling intercurrent events such as:

    - A composite strategy in which pediatric subjects who experience the intercurrent event are considered to have an unfavorable outcome (e.g., to have not achieved remission).

    - A treatment policy strategy in which outcomes are collected after the intercurrent event and used in analyses.

  - Sponsors should continue to follow pediatric subjects after the occurrence of all intercurrent events, regardless of the strategy used in the primary analysis, to facilitate important analyses using a treatment policy strategy. The protocol should distinguish between reasons for treatment discontinuation and reasons for study withdrawal and should include plans to follow pediatric subjects for collection of relevant data after treatment discontinuation and use of rescue therapies.

- Sponsors should prespecify sensitivity analyses to evaluate whether the results from the primary and secondary analyses are robust to the missing data assumptions. These sensitivity analyses should comprehensively explore the space of plausible assumptions.

3. Future Clinical Outcome Assessment Development[23,24]

Sponsors wishing to develop additional novel clinical outcome assessment (COA) measures (or adapt existing instruments for use in pediatric UC or CD subjects) to assess concepts that are

[22] See the International Council for Harmonisation guidance for industry *E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials* (May 2021).

[23] For general recommendations regarding patient-reported outcome (PRO) assessments (as well as information relevant for other clinical outcome assessments), see the guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims* (December 2009) (2009 Final PRO guidance).

[24] See the FDA Patient-Focused Drug Development (PFDD) Guidance Series for Enhancing the Incorporation of the Patient's Voice in Medical Product Development and Regulatory Decision Making web page at https://www.fda.gov/drugs/development-approval-process-drugs/fda-patient-focused-drug-development-guidance-series-enhancing-incorporation-patients-voice-medical. These guidances are part of FDA's PFDD efforts in accordance with the 21st Century Cures Act and the Food and Drug Administration Reauthorization Act of 2017 Title I. When final, the PFDD guidance series will replace the 2009 Final PRO guidance.

relevant to pediatric subjects with UC or CD but are not captured within the mMS or PCDAI for UC and CD, respectively, can submit a COA development proposal to the Division for review.

D. Safety considerations

Sponsors developing drugs for the treatment of pediatric UC or CD should consider the following:

- An adequate characterization of safety in pediatric subjects is needed to support a benefit-risk assessment for drugs for the treatment of pediatric UC or CD. Safety information from adult subjects may help to inform risk in pediatric subjects but cannot replace the need for primary safety data in pediatric subjects.

  - Sponsors seeking to use real-world evidence to provide supportive safety data should discuss their proposed approaches with the appropriate review division early in the pediatric development program. In most cases, sponsors should use randomized blinded data to inform the risk assessment of a drug for the treatment of pediatric UC or CD.

- Sponsors should prospectively plan for safety analyses to compare treatment groups with respect to risk (e.g., with a risk difference, relative risk, rate ratio, hazard ratio) along with a confidence interval for the chosen metric to help quantify the uncertainty in the treatment comparison. Additionally, we recommend a prospectively planned comparison with adult trials. Any analyses of integrated data from multiple studies should be stratified by study.

- Corticosteroid weaning should be permitted, standardized in the protocol, and encouraged at the earliest feasible time point after randomization.

- FDA has previously recommended a washout period for prior therapies of five half-lives, or an undetectable serum level (when available). To promote timely enrollment of pediatric subjects with active disease, reduce the potential need for escalation of corticosteroids as *bridging* therapy, and reduce the potential loss of study eligibility, sponsors may propose shorter washout periods, with appropriate justification.

  - A sponsor proposing a shorter washout period should acknowledge within the protocol and informed consent the potential increased risk of adverse events (e.g., serious infections) in the early portion of the study and include appropriate close monitoring and risk mitigation plans.

- For drugs intended for long-term treatment, such as for pediatric UC or CD, a sufficient number of pediatric subjects should be exposed to the to-be-marketed dosing regimen (selected induction dose followed by selected maintenance dose, when applicable) for at least 52 weeks to characterize the safety profile of the drug.

- Drug-specific considerations may alter the minimum acceptable size of the safety database, including whether the drug in question is a new molecular entity or has relevant supportive safety data from other populations, the known and anticipated adverse events of the drug and drug class, and nonclinical findings.

- For studies of therapeutic protein products, such as monoclonal antibodies, sponsors should consider recommendations in the guidance for industry *Immunogenicity Assessment for Therapeutic Protein Products* (August 2014). Sponsors should evaluate neutralizing capabilities of antidrug antibodies and their impact on clinical efficacy and safety.

REFERENCES

Literature

Greuter T, Bertoldo F, Rechner R, Straumann A, Biedermann L, Zeitz J, Misselwitz B, Scharl M, Rogler G, Safroneeva E, Ali RAR, Braegger C, Heyland K, Mueller P, Nydegger A, Petit LM, Schibli S, Furlano RI, Spalinger J, Schappi M, Zamora S, Froehlich F, Herzog D, Schoepfer AM, Vavricka SR, and Swiss IBD Cohort Study Group, 2017, Extraintestinal Manifestations of Pediatric Inflammatory Bowel Disease: Prevalence, Presentation, and Anti-TNF Treatment, J Pediatr Gastroenterol Nutr, 65(2):200–206.

Turner D, Levine A, Walters TD, Focht G, Otley A, Navas Lopez V, Koletzko S, Baldassano R, Mack D, Hyams J, and Griffiths AM, 2017, Which PCDAI Version Best Reflects Intestinal Inflammation in Pediatric Crohn Disease?, J Pediatr Gastroenterol Nutr, 64(2):254–260.

Torres J, Mehandru S, Colombel JF, and Peyrin-Biroulet L, 2017, Crohn's Disease, Lancet, 389(10080):1741–1755.

Ungaro R, Mehandru S, Allen PB, Peyrin-Biroulet L, and Colombel JF, 2017, Ulcerative Colitis, Lancet, 389(10080):1756-1770.

Guidances[1]

Draft guidance for industry *Adjusting for Covariates in Randomized Clinical Trials* (May 2021)[2]

Draft guidance for industry *Crohn's Disease: Developing Drugs for Treatment* (April 2022)[3]

Draft guidance for industry *Meta-Analyses of Randomized Controlled Clinical Trials to Evaluate the Safety of Human Drugs or Biological Products* (November 2018)[4]

Draft guidance for industry *Ulcerative Colitis: Developing Drugs for Treatment* (April 2022)[5]

Guidance for industry and FDA staff *Qualification Process for Drug Development Tools* (November 2020)

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

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[3] When final, this guidance will represent the FDA's current thinking on this topic.

[4] When final, this guidance will represent the FDA's current thinking on this topic.

[5] When final, this guidance will represent the FDA's current thinking on this topic.

Guidance for industry *Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs* (November 2020)

Guidance for industry, FDA staff, and other stakeholders *Patient-Focused Drug Development: Collecting Comprehensive and Representative Input* (June 2020)

Guidance for industry *Immunogenicity Assessment for Therapeutic Protein Products* (August 2014)

Guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims* (December 2009)

Guidance for industry *Premarketing Risk Assessment* (March 2005)

International Council for Harmonisation guidance for industry *E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials* (May 2021)

APPENDIX[1]

The modified Mayo Score (mMS) (see Table 1) is a composite endpoint consisting of rectal bleeding, stool frequency, and endoscopy subscores, adapted from the originally published Mayo Score. Table 2 provides an example of instructions for subjects to accurately capture patient-reported outcome data for stool frequency and rectal bleeding subscores.

Table 1. Modified Mayo Score (mMS)

mMS Subscores by Category	
Stool Frequency*	
0	Normal number of stools for this subject
1	1–2 more stools than normal
2	3–4 more stools than normal
3	5 or more stools more than normal
Rectal Bleeding**	
0	No blood seen
1	Stool with streaks of blood
2	Stool with more than streaks of blood
3	Blood alone passed
Endoscopy	
0	Normal appearance of mucosa
1	Mild disease (erythema, decreased vascular pattern, no friability)
2	Moderate disease (marked erythema, absent vascular pattern, friability, erosions)
3	Severe disease (spontaneous bleeding, ulcerations)

* Each subject provides own baseline against which to compare the degree of abnormality in stool frequency.
** Represents the worst bleeding score for that day.

[1] For this Appendix, training and instructions for capturing patient-reported outcome data can also be used by parents, caretakers, and guardians of pediatric patients.

Table 2. Example of Standardized Instructions for Recording Number of Stools and Worst Rectal Bleeding (Each in a 24-Hour Period)[*]

Category of Instructions	Specific Instructions to Subjects
Definition of *stool frequency*	• Subjects should be instructed to report the number of trips to the toilet when the subject had a bowel movement (including passing feces, blood alone, blood and mucus, or mucus only).
Reference remission stool frequency (in a 24-hour period)	• The subject should be asked to identify at the screening visit how many stools the subject had in a 24-hour period when in remission from ulcerative colitis (UC). • If the subject does not report achieving remission, then the subject should be asked to identify the number of stools had in a 24-hour period before initial onset of signs and symptoms of UC. If the subject has not experienced remission, this value will be used to calculate the stool frequency endpoint. — Sponsors should record if the reference remission stool frequency is based on reported stool frequency when the subject was in remission or reported stool frequency before initial onset of signs and symptoms of UC. — Sponsors should collect both the remission and pre-UC stool frequency at baseline when feasible. This allows exploration of the natural history of prediagnosis stool frequency versus remission stool frequency.
Most severe category of rectal bleeding (in a given 24-hour period)	• Subjects should be instructed to indicate the most severe category that describes the amount of blood they had in their stools for a given 24-hour period. • Categories of rectal bleeding should be defined as follows (in order of increasing severity): — Not applicable; no bowel movement[**] — No blood seen — Stool has streaks of blood — Stool has more than just streaks of blood — Blood alone passed
Completion of event log or diary	• Subjects should be trained on the completion of the event log or diary. • The instructions for completion of the stool frequency and rectal bleeding assessments should be incorporated into the event log or diary for ready reference by the subject.
Recording of rectal bleeding and stool frequency assessments	• Subjects should be directed to capture their rectal bleeding and stool frequency assessments in event logs or daily diaries for a minimum of 7 days before each visit.

[*] FDA encourages sponsors to propose an electronic data collection method (e.g., electronic diary, web-based system) as an alternative to pen and paper data collection. If an electronic data collection method is proposed, sponsors should provide site training and instructions for subjects and investigators. To minimize missing data, sponsors should implement a web- or paper-based backup plan and reminder or alarm functions on the electronic device. To ensure proper recall period for the assessment, sponsors should consider exploring inclusion of reasonable lock-out times before and after which no entries can be made.

** If the event log or diary is set up to include the option of "no bowel movement occurred," then this rectal bleeding response is not necessary.

The Pediatric Crohn's Disease Activity Index (see Table 3), a weighted index comprising 11 clinical and laboratory variables that estimate disease severity in Crohn's disease (CD), has been the most commonly used tool in clinical studies intended to support approval of CD treatments. Table 4 outlines the components of the Simple Endoscopic Score for Crohn's Disease, a scoring algorithm that can be used to measure endoscopic features of CD.

Table 3. Pediatric Crohn's Disease Activity Index (PCDAI)

History	Score	Laboratory	Score
Abdominal pain:		Hematocrit (%):	
• None	0	• <10 years old	
• Mild – brief, does not interfere with activities	5	— >33	0
		— 28-32	2.5
• Moderate/severe – daily, longer lasting, affects activities, nocturnal	10	— <28	5
		• 11-14 years old (male)	
		— ≥35	0
		— 30-34	2.5
Stools (per day):		— <30	5
• 0-1 liquid stools, no blood	0	• 15-19 years old (male)	
• Up to 2 semi-formed with small blood, or 2-5 liquid	5	— ≥37	0
		— 32-36	2.5
• Gross bleeding, or ≥ 6 liquid, or nocturnal diarrhea	10	— <32	5
		• 11-19 years old (female)	
		— ≥34	0
		— 29-33	2.5
		— <29	5
		Erythrocyte sedimentation rate (millimeters/hour)	
		— <20	0
		— 20-50	2.5
		— >50	5
		Albumin (grams/deciliter)	
		— ≥3.5	0
		— 3.1-3.4	5
		— ≤3.0	10

continued

Table 3, continued

Examination	Score	Examination	Score
Weight: • Weight gain or voluntary weight stable/loss • Involuntary weight stable, weight loss 1-9% • Weight loss ≥10%	 0 5 10	Height: • At diagnosis — <1 channel decrease — ≥1, <2 channel decrease — ≥2 channel decrease • Follow-up — Height velocity ≥ -1 standard deviation (SD) — Height velocity < -1 SD, > -2 SD — Height velocity ≤ -2 SD	 0 5 10 0 5 10
Abdomen: • No tenderness, no mass • Tenderness, or mass without tenderness • Tenderness, involuntary guarding, definite mass	 0 5 10	Perirectal disease • None, asymptomatic tags • 1-2 indolent fistula, scant drainage, no tenderness • Active fistula, drainage, tenderness, or abscess	 0 5 10
Extra-intestinal manifestations: • Fever ≥38.5ºC for 3 days over past week, definite arthritis, uveitis, erythema nodosum, pyoderma gangrenosum) — None — 1 — ≥2	 0 5 10		
Patient Functioning, General Well-Being	**Score**		
• No limitation of activities, well • Occasional difficulty in maintaining age-appropriate activities, below par • Frequent limitation of activity, very poor	0 5 10		

Total Score: _____

Adapted from Hyams JS, Ferry GD, Mandel FS, Gryboski JD, Kibort PM, Kirschner BS, Griffiths AM, Katz AJ, Grand RJ, Boyle JT, Michener WM, Levy JS, and Lesser ML, 1991, Development and Validation of a Pediatric Crohn's Disease Activity Index, J Pediatr Gastroenterol Nutr, 12(4):439–447.

Table 4. Simple Endoscopic Score for Crohn's Disease (SES-CD)

Variable	SES-CD Values			
	0	1	2	3
Size of ulcers	None	Aphthous ulcers (diameter 0.1 to 0.5 centimeters (cm))	Large ulcers (diameter 0.5 to 2 cm)	Very large ulcers (diameter > 2 cm)
Ulcerated surface	None	< 10%	10-30%	> 30%
Affected surface	Unaffected segment	< 50%	50-75%	>75%
Presence of narrowing	None	Single, can be passed	Multiple, can be passed	Cannot be passed

Adapted from Daperno M, D'Haens G, Van Assche G, Baert F, Bulois P, Maunoury V, Sostegni R, Rocca R, Pera A, Gevers A, Mary JY, Colombel JF, and Rutgeerts P, 2004, Development and Validation of a New, Simplified Endoscopic Activity Score for Crohn's Disease: The SES-CD, Gastrointest Endosc, 60(4):505–512.