Pediatric Gastroesophageal Reflux 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DRAFT GUIDANCE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)

October 2017
Clinical/Medical

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Pediatric Gastroesophageal Reflux 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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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 assist sponsors in the clinical development of drugs for the treatment of gastroesophageal reflux disease (GERD) in the pediatric population, encompassing infants, children, and adolescents. Specifically, this guidance addresses the Food and Drug Administration's (FDA's) current thinking regarding clinical presentation by age and disease, study populations, endpoints, and clinical pharmacology issues affecting dosing. This draft guidance is intended to serve as a focus for continued discussions among the Division of Gastroenterology and Inborn Errors Products, pharmaceutical sponsors, the academic community, and the public.[2]

This guidance does not contain discussion of the general issues of statistical analysis. That topic is addressed in the ICH guidance for industry *E9 Statistical Principles for Clinical Trials.*[3]

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

[2] 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 GERD.

[3] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance web page at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

Sponsors are encouraged to discuss the specifics of pediatric programs as early as is feasible with the division on a case-by-case basis because sponsors are required to submit pediatric study plans under the Pediatric Research Equity Act no later than 60 days after an end-of-phase 2 meeting.[4]

The following guidances for industry provide additional information:

- Draft guidance for industry *General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products*[5]
- Draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans*[6]
- Guidance for industry *Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications*
- Guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*

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

II. BACKGROUND OF PEDIATRIC GERD

A. Physiology, Natural History, and Definitions of Gastroesophageal Reflux and Gastroesophageal Reflux Disease in Pediatric Patients

There are several anatomical structures that protect a patient against the development of reflux of acidic contents of the stomach (i.e., gastroesophageal reflux (GER)). This *antireflux barrier* consists of the lower esophageal sphincter (LES), the crural diaphragm, and the phrenoesophageal ligament. Non-erosive reflux disease (i.e., GER disease, or GERD) in the pediatric patient is defined by the presence of troublesome symptoms caused by the reflux of gastric contents and by the absence of mucosal breaks observed during endoscopy. It is also referred to as symptomatic GERD. Some of the pathogenic factors that can lead to the

[4] Or such other time as may be agreed upon between FDA and the sponsor (section 505B(e)(2)(A) of the Federal Food, Drug, and Cosmetic Act (FD&C Act); 21 U.S.C. 355c(e)(2)(A)). For further information, FDA recommends sponsors refer to section 505B of the FD&C Act, and to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans*. 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.

[6] Ibid.

development of GERD include transient LES relaxation, impaired esophageal clearance, delayed gastric emptying, and increased gastric volume or pressure. GERD may progress to erosive disease (eGERD, including erosive esophagitis). Endoscopic classifications are used to grade the severity of erosive disease, by the presence and extent of mucosal breaks or erosions (Sherman, Hassall, et al. 2009).

As children grow older, they appear to naturally regurgitate less of their feedings. When one examines the prevalence of regurgitation by quartiles of a year, infants at 4 to 6 months of age have the highest rates of regurgitation (67 percent at least once per day; 23 percent at least four times per day). For 0- to 3-month olds, 51 percent regurgitate at least once per day and 17 percent regurgitate at least four times per day. In 7- to 9-month olds, the prevalence drops to 21 percent of children regurgitating at least once per day and 7 percent of children regurgitating at least four times per day. At 10 to 12 months old the prevalence drops further to 5 percent at least once per day and 3 percent at least four times per day (Nelson, Chen, et al. 1997). By 2 years of age, this percentage drops to less than 1 percent (Martin, Pratt, et al. 2002). When one examines the incidence rates in children ages 1 to 17, there is a U-shaped curve with the nadir at ages 8 to 9 (approximately 0.6 per 1,000 patient years). The incidence is highest at ages 16 to 17 (approximately 2 per 1,000 patient years), closer to that of adults, and second highest at age 1 (approximately 1.5 per 1,000 patient years) (Ruigómez, Wallander, et al. 2010).

B. Clinical Features of GER and GERD

Practitioners must distinguish between GER and GERD. GERD is GER with pathological signs and symptoms and/or complications, including the development of erosive esophagitis as a sequelae of GERD. The clinical features of GERD vary with age and include regurgitation, vomiting, food refusal, growth effects, and, in patients able to complain, epigastric discomfort, acidic taste, heartburn, and abdominal pain. Diagnosis based on signs and symptoms is more difficult in the younger age groups, while in adolescence, symptoms alone may be sufficient to make the initial diagnosis of GERD. In patients who can accurately communicate these typical signs and symptoms (without pathological features (e.g., weight loss, failure to thrive)), currently the standard of care in a community setting would be an empiric trial of medication. However, to confirm the existence of erosions, endoscopy would be required to diagnose eGERD, even in adolescents.

1. Neonates (Birth to 1 Month)

Nonspecific signs and symptoms of GER can occur within the neonatal period. GER may be a normal phenomenon in neonates and infants because of their age-specific body position and high fluid intake (Poets, Brockman, et al. 2011). Clinical signs presumed to be associated, without confirmation of pathobiology, with GERD in the neonatal period include apnea, failure to thrive, and pulmonary complications, particularly in preterm infants. Whether or not these clinical signs and symptoms indicate a diagnosis of GERD is unclear (Abu Jawdeh and Martin 2013).

Signs and symptoms of GERD may be acid-mediated or non-acid-mediated. Acid-mediated GERD is similar to GERD seen in older infants and other pediatric age groups. Non-acid-mediated GERD symptoms may be because of poor motility of gastric contents and is not improved by acid-limiting drugs. The pathogenic role of non-acid regurgitation requires further study before a relationship, if any, can be established with neonatal presentations of GERD and its complications.

2. Infants (1 Month to Younger Than 1 Year)

GER is common in infants. Up to 67 percent of 4-month-old infants have regurgitation more than once a day (Campanozzi, Boccia, et al. 2009). Regurgitation will resolve in most infants by 10 to 12 months of age and can be treated effectively with lifestyle changes alone (e.g., thickening feeds), without the need for pharmacologic therapy (Campanozzi, Boccia, et al. 2009). Infants with GERD will demonstrate regurgitation, poor weight gain, and refusal to feed. The presentation of erosive esophagitis in this population is rare, based on epidemiological studies, and, where it exists, it is potentially related to pathogenic causes such as viral and bacterial infections, instead of GER. The signs and symptoms of GERD in infants can be caused by the effect of acid and non-acid reflux on the esophagus. Because GERD in infants has many etiologies and presents diagnostic difficulties, sponsors who wish to develop drugs for this indication should request a meeting with FDA to discuss clinical trial designs.

3. Children (1 Year to Younger Than 12 Years)

GERD may present as eGERD in this age cohort. Eliciting accurate histories of pain and location of pain may be difficult in children younger than 8 to 12 years of age (Vandenplas, Rudolph, et al. 2009). In contrast to infants, toddlers and school age children may complain of abdominal pain, heartburn, respiratory problems including cough, feeding problems including odynophagia, dysphagia, weight loss, regurgitation, vomiting, and food refusal. In children aged 1 year to 5 years, cough, food refusal, and regurgitation/vomiting are more common than in older children. Older children are more likely to complain of epigastric pain or heartburn and regurgitation (Sherman, Hassall, et al. 2009). Signs and symptoms of eGERD are similar to those described for GERD, but also include endoscopic findings of esophageal erosions

4. Adolescents (12 Years to 17 Years)

The clinical features of GERD are similar to those seen in adults. The otherwise healthy adolescent should be able to describe symptoms of heartburn and the location of abdominal pain. Thus, a diagnosis of GERD can be made when substernal, burning chest pain with or without regurgitation presents as primary symptoms. Signs and symptoms of eGERD are similar to those described for GERD, but also include endoscopic findings of esophageal erosions, in addition to possible vomiting, hematemesis, and weight loss.

III. DRUG DEVELOPMENT STRATEGY: PARADIGMS AND REGULATORY CONSIDERATIONS

A. Establishing Efficacy-Regulatory Requirements in Different Age Cohorts

1. Age Cohorts

Sponsors should address the entire pediatric age range (birth through 16 years). If physiologic categories or groupings based upon systems ontogeny are used, they should be supported with scientific and developmental data. Age cohort determination should be based on clinical and biological factors and drug characteristics. For example, healing of erosive esophagitis should be studied in pediatric patients 1 month to 17 years of age (as the disease is rare in neonates).[7]

To ensure adequate characterization of pharmacokinetics, pharmacodynamics, safety, and/or effectiveness for dosing recommendations in pediatric patients, age cohorts should be defined before a pediatric study is conducted so that a sufficient number of patients representing each age cohort will be enrolled in the study. For example, for development of proton pump inhibitors (PPIs) for healing of erosive esophagitis, patients generally should be stratified into four age cohorts: 1 to 11 months, 1 to 5 years, 6 to 11 years, and 12 to 17 years. For patients aged 1 to 11 months, the ontogeny of both metabolic enzymes (e.g., CYP2C19, a primary metabolic enzyme for most PPIs) and the proton pump should be considered to determine the appropriate stratification. Because age stratification takes into consideration both the developmental biology and pharmacology, age cohorts can differ for drugs with a different mechanism of action even though they may be for the same indication.

2. Pediatric Extrapolation

Extrapolation of efficacy from adult populations to pediatric populations may be appropriate if the course of the disease and the effects of the drug are sufficiently similar in adult and pediatric patients.[8] Extrapolation of efficacy from one pediatric age group to another pediatric age group also may be appropriate.[9] Although efficacy can be extrapolated, additional safety and dosing information generally will need to be collected.[10]

[7] Because erosive esophagitis is rare in neonates, the requirement of studies for the treatment of erosive esophagitis would be waived in the neonatal age cohort.

[8] See section 505B(a)(2)(B)(i) of the FD&C Act; 21 U.S.C. 355c(a)(2)(B(i).

[9] See section 505B(a)(2)(B)(ii) of the FD&C Act; 21 U.S.C. 355c(a)(2)(B(ii).

[10] See 21 CFR 201.80(f)(9)(iv). See Dunne, Rodriguez, et al. 2011 and the draft guidance for industry *General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products* for information on extrapolation in pediatric settings in general.

If a sponsor proposes to rely upon pediatric extrapolation, a scientific rationale, including sufficient justification and supporting data, should be submitted to the Agency and, when one is required under section 505B of the Federal Food, Drug, and Cosmetic Act, should also be included in a pediatric study plan.[11] Represented in Table 1 are examples of GERD-related indications and the Agency's current thinking on the potential appropriateness of pediatric extrapolation in those cases.

Table 1: Potential for Pediatric Extrapolation

Proposed Indication	Patient Age Group	Potential for Pediatric Extrapolation
Healing of erosive esophagitis	Birth to < 1 month of age	Pediatric extrapolation not likely relevant for this age group, as this disease is rare in the neonatal age group.
	1 month to 17 years of age	Pediatric extrapolation may be acceptable depending on the totality of available information on the specific drug and the class.
Maintenance of healing of erosive esophagitis	Birth to < 1 month of age	Pediatric extrapolation not likely relevant for this age group, as this disease is rare in the neonatal age group.
	1 month to 17 years of age	The Agency is currently unlikely to accept pediatric extrapolation for this indication because it is uncertain whether pediatric patients require a maintenance period after healing of erosive esophagitis is established. Furthermore, if maintenance treatment is required, the duration required for such treatment is unclear.
GERD	Birth to 11 months of age	The Agency currently does not consider pediatric extrapolation appropriate for drugs that are targeted at acid blockage, such as PPIs, in patients < 1 year of age. Trials in this age group for PPIs have not demonstrated efficacy and the signs and symptoms of GERD in patients < 1 year of age may not be solely due to increased acid. Extrapolation may be considered for drugs with a different mode of action, taking into consideration its effect on the presentation of signs and symptoms in this age group.
	1 year to 17 years of age	Whether the Agency would accept pediatric extrapolation for this indication depends in part on whether the mechanism of action of the specific drug will support that the response to treatment will be the same between the populations involved in potential extrapolation. Furthermore, the ability of the patient or the observer/caregiver (for children who are too young to self-report) to reliably recognize, report, and measure heartburn and related symptoms or behaviors thought to be associated with those symptoms in young children, would affect the appropriateness of pediatric extrapolation.

[11] For additional information, see the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans.*

B. Dose Finding

Adequate evaluation of an appropriate dose range is an integral part of developing scientifically sound and rational dosing recommendations in pediatrics. In general, it is important to study a wide range of doses to establish dose/exposure-response over a wide range and at the same time gather safety data at higher doses. As appropriate, the use of modeling and simulation and/or clinical trial simulation is recommended for designing pediatric clinical trials and for selecting dose. It is also possible to use adaptive study designs for dose selection.[12] Depending on the level of extrapolation, there are in general three different approaches for obtaining the data that are needed to support dose selection in pediatric patients:

(1) **Pharmacokinetic (PK) and efficacy approach.** If neither disease progression nor response to intervention is expected to be similar in pediatrics and adults, then extrapolation of efficacy from adults to pediatric population is not possible. In such a case, adequate dose-ranging studies should be conducted in pediatric patients to establish dosing, followed by conducting efficacy and safety trials at the identified doses.[13] It is recommended to collect PK data in these trials to establish the exposure-response relationship to aid in dose optimization in pediatric patients.

(2) **PK and pharmacodynamic approach.** This approach of dose finding is applicable when disease progression and response to intervention are similar in pediatrics and adults, yet it is not known whether the exposure-response relationship between adults and pediatric patients is similar. In such a case, the exposure-response relationship in adults should be well-characterized and accepted by the Agency. Note that the response may be measured by an appropriate clinical measure or a biomarker (e.g., percent time pH greater than 4 in 24 hours). An adequate dose-ranging study is then conducted in pediatric patients to select doses in children that achieve the target effect. In this regard, the dose range to be covered should take into consideration the potential or observed differences in both exposure and response.[14] It is recommended to collect PK data in these trials to establish the exposure-response relationship to aid in dose optimization in pediatric patients.

(3) **PK-only approach.** This dose-selection approach is applicable when disease progression and response to intervention as well as the exposure-response are similar in pediatrics and adults (full extrapolation). In such a case, dose-ranging studies in pediatrics are not needed. Adequate PK studies in pediatrics are conducted to select a dose in pediatric patients that provides exposures similar to that of the approved doses in

[12] See the draft guidance for industry *Adaptive Design Clinical Trials for Drugs and Biologics.* When final, this guidance will represent the FDA's current thinking on this topic.

[13] See the draft guidance for industry *General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products*. When final, this guidance will represent the FDA's current thinking on this topic.

[14] See the draft guidance for industry *General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products*.

adults. PK simulations should be performed to identify the pediatric dose that is expected to produce exposures similar to adults.

The precision of the PK parameters is critical when designing the pediatric PK studies. For pediatric studies that are vital for dose selection, sponsors are recommended to prospectively design the pediatric studies with an adequate sample size to obtain precise estimates of PK parameters (Wang, Jadhav, et al. 2012). Prior knowledge of disease, exposure from adults, and other relevant pediatric data can be used to derive the sample size for pediatric studies. See the draft guidance for industry *General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products* for more details.

C. Establishing Safety-Regulatory Requirements

1. Nonclinical

The nonclinical safety assessment to support marketing approval should comply with recommendations outlined in the ICH guidance for industry *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals.* Additional information on the timing and role of nonclinical studies to support the safety evaluation of pharmaceuticals for the pediatric population is available in the guidance for industry *Nonclinical Safety Evaluation of Pediatric Drug Products*. Attention should be paid to providing sufficient nonclinical data to support the youngest age group and maximum doses and duration of treatment for patients expected to be enrolled in pediatric studies.

2. Clinical

There must be adequate safety data for all claimed indications in all relevant patient ages for which the drug would be approved for use.[15]

Although the total safety database contributes to the safety database, there should be sufficient data at the highest dose to support approval of that dose.

Ideally, safety data should be collected for all indications. Although additional safety information should be collected even when pediatric extrapolation of efficacy is appropriate, safety data obtained for one indication may support safety in another indication if the patient populations are sufficiently similar, and if the doses and duration of treatment studied are comparable. For example, the safety data obtained in patients 12 years of age and older for the maintenance of healing of erosive esophagitis may be able to support the safety profile for the acute treatment of erosive esophagitis in patients 12 years of age and older, provided that the patient populations were sufficiently similar, that the dose and frequency in the maintenance of healing of erosive esophagitis safety database were at least as high and as frequent as would be in the acute treatment of erosive esophagitis indication, and that the duration of use in the maintenance of healing of erosive esophagitis safety database was at least as long as would be needed for the acute treatment of erosive esophagitis indication.

[15] See section 505B(a)(2)(A)(i) of the FD&C Act; 21 U.S.C. 355c(a)(2)(A)(i).

IV. CLINICAL TRIAL DESIGN CONSIDERATIONS

This section presents issues for sponsors to consider in their drug development programs to establish efficacy of a new drug for the treatment of pediatric GERD. An overview of efficacy and the need for pediatric efficacy trials is first presented, followed by details specific to pediatric GERD.

Establishing efficacy for a drug requires "substantial evidence," consisting of "adequate and well-controlled investigations."[16] The details are not discussed here, and additional detailed guidances on clinical trials should be consulted when designing a pediatric drug development program. In cases where FDA determines that extrapolation of efficacy is acceptable (see section III.A.2., Pediatric Extrapolation), a fully powered trial, designed with efficacy endpoints for all pediatric age groups, may not be needed. This section provides guidance for when extrapolation cannot be used and a phase 3 trial is needed. For further guidance on use of extrapolation and the approach to pediatric studies, see the draft guidance for industry *General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products*.

A. Erosive GERD

For an indication in treatment of eGERD, such as healing of erosions, the study population should consist entirely of patients with esophageal erosions secondary to GERD. Because eGERD in infants is rare and potentially related to pathogenic causes such as viral and bacterial infections, and because of the inability to accurately establish a diagnosis in neonates, neonates generally should be excluded from clinical trials for an eGERD indication. The diagnosis of eGERD should be established through direct visualization of one or more esophageal erosions on upper endoscopy. Endoscopic classifications are used to grade the severity of erosive disease by the presence and extent of mucosal breaks (erosions). Other etiologies that can cause erosions should be excluded, including Crohn's esophagitis, eosinophilic esophagitis, and esophagitis secondary to infection, toxins, and caustics. In children with severe neurodevelopmental delay, there may be other etiologies for presumed GERD-related signs and symptoms. Endoscopic biopsy procedures should be described in the protocol as to biopsy location, number, method, and adjudication (ideally a panel of independent experts to adjudicate the diagnosis).

For an indication of treatment of eGERD or erosions, the primary endpoint should be healing of erosions, which should be assessed at 8 to 12 weeks using the same diagnostic procedure(s) used to establish the diagnosis at baseline. A primary endpoint of symptom improvement alone is not acceptable, because there is a weak relationship between the existence of erosions and the presence of symptoms. However, it may be possible to obtain an additional indication of symptom improvement if the symptom assessment instrument is included as a primary or key secondary endpoint in conjunction with endoscopic and histologic healing.

[16] For establishing efficacy of a drug, see 21 CFR 314.126. See also generally the guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*.

As a general matter, a patient-reported outcome (PRO) symptom assessment instrument measures the core symptoms of GERD in children who are old enough to reliably self-report their symptoms. An observer-reported outcome (ObsRO) assessment will be needed to assess efficacy for children who are unable to self-report.[17]

B. Symptomatic GERD

Obtaining an indication for GERD in children is potentially problematic because of the variety of working definitions of GERD, which include the following: (1) *suspected* (symptoms without performing endoscopy); (2) signs and symptoms without erosions seen on endoscopy; and (3) signs and symptoms without inflammation seen on endoscopy. The Agency prefers the documented non-erosion definition (number 2, above) because this allows the potential extrapolation from adult data unless the sponsor can adequately justify not using it. Currently, biopsy evidence of inflammation is assessed as part of an endoscopy (in clinical practice) but used to differentiate between GERD and other diseases that have mucosal characteristics (i.e., eosinophilic esophagitis) that also can be responsive to PPI therapy. Therefore, the protocol should define GERD for the purposes of the trial. Children with other etiologies of GERD (*Helicobacter pylori*, Crohn's, eosinophilic esophagitis, and others that may require biopsy) should be excluded from the trial population to exclude any potential for bias in the interpretation of the study results.

For an indication of treatment of GERD, a treatment duration of 8 to 12 weeks is acceptable.

Given the central role of symptoms in GERD, the ability of a drug to improve symptoms is critical to its approval. Consequently, the primary endpoint should include a PRO measure that measures signs and symptoms for older children and an ObsRO measure in infants and younger children. If an alternative endpoint, such as weight gain, is considered appropriate for the population selected for study, these PRO and ObsRO measures should be included as important secondary endpoints.

There are unique considerations when developing instruments to measure signs and symptoms in children ranging in age from infants to adolescents; further information can be found in the guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*. A child's self-report of symptoms using a PRO instrument is preferred at the age when children can provide valid and reliable self-report. However, the minimum age of self-report also depends, in part, on the complexity of what is being measured (e.g., comprehension of the concept) and how it is being measured (e.g., vocabulary being used, duration of recall required). Children as young as 6 to 7 years of age may be able to respond reliably to PRO instruments that ask simple questions using age-appropriate language (Matza, Patrick, et al. 2013).

It is important to note that some children may be able to read but not understand concepts, while others may be able to understand concepts but not read on their own. Interviewer (e.g., parent,

[17] See the guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*.

computer-assisted) administration of the instrument may be considered for young children who cannot yet read. Although the measure can be developed as an interviewer-administered instrument, the administration should be standardized to minimize variation across interviewers, and any influence on the child's response or alteration of the child's response by the interviewer should be avoided. Children's understanding and interest in completion of the instrument may be enhanced by using illustrations and/or platforms for administration that children may already be familiar with. Daily diaries or current state assessments of symptoms in children are generally preferred over instruments with longer recall periods.

As previously stated, an ObsRO measure will be needed to evaluate infants and young children who are not able to report for themselves. Observers (e.g., parents, caregivers) can only validly report on signs and behaviors that they can directly observe and should not be asked to rate an unobservable concept (e.g., abdominal pain) or influence the child's responses in any way. Therefore, ObsRO instruments should only include questions related to signs and behaviors (e.g., crying, vomiting) rather than symptoms (e.g., pain).

1. Adolescents (12 Years to Younger Than 18 Years)

The primary endpoint in adolescents with GERD should be symptom-based using a PRO instrument. In this case, an acceptable primary endpoint could be an evaluation of symptom-free days of heartburn, which has been used as the basis of approval for drugs to treat GERD in adults.

2. Children (6 Years to 11 Years)

Children with GERD in this age group may be able to reliably report their symptoms, but the extent to which they can do so reliably may vary across this age range such that the minimum age of reliable self-report should be evaluated and discussed with the Agency. Children with GERD in this age group may also present differently than older children with the condition. The preferred primary endpoint is a measure of symptoms using a PRO, if appropriate, or a measure of observable signs and behaviors using an ObsRO. The primary endpoint should be assessed in the same way at enrollment and end of treatment.

3. Children (1 Year to 5 Years)

In this age group, the main issue is limited communicative ability and a different clinical presentation compared to older children, adolescents, and adults. The primary endpoint should be assessed using an ObsRO instrument that asks the observer (e.g., parent or caregiver) only about observable signs and behaviors. A well-defined and reliable ObsRO instrument for this age group would be useful for efficacy determination. The primary endpoint should be assessed in the same way at enrollment and end of treatment.

4. Infants (1 Month to Younger Than 1 Year)

Diagnosing and treating GERD in infants is challenging. Infant GERD is not well-characterized, and diagnostic problems create issues with identifying an appropriate target population for

clinical trials. Because of the inability to accurately establish a diagnosis in neonates, this age group should be excluded from clinical trials. The natural history of GERD in infants is not well-understood, such as the effect of normal maturation on GERD resolution. Symptoms of GERD are difficult to measure in infants and nonspecific. In infants, GERD signs and symptoms overlap with other conditions such as colic or food allergy, and this presents a unique challenge in the setting of a clinical trial. Sponsors planning to conduct clinical trials of GERD in infants should first reach agreement with FDA on an acceptable disease definition and outcome measures. Primary outcome measures related to the drug's specific mechanism of action may be acceptable if adequately justified and supported with data.

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Guidances[18]

Draft guidance for industry *Adaptive Design Clinical Trials for Drugs and Biologics*

Draft guidance for industry *General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products*

Draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans*

Guidance for industry *Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications*

Guidance for industry *Nonclinical Safety Evaluation of Pediatric Drug Products*

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

Guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*

ICH guidance for industry *M3(R2) Nonclinical Safety Studies for the Human Clinical Trials and Marketing Authorization for Pharmaceuticals*

[18] Guidances can be found on the FDA Drugs guidance web page at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.