

DOCUMENT INFORMATION PAGE

This page is for FDA internal use only. Do **NOT** send this page with the letter.

Application #(s): IND/NDA #####

Communication Type:	Correspondence
Communication Group:	Pediatric Exclusivity
Communication Name:	Pediatric Written Request
Communication ID:	COR-PEDEX-01

Drafted by:	
Clearance History:	
Finalized:	
Filename:	

Signatory Authority:	Office Director or Deputy
Use Statement:	Use to send the applicant a 'Written Request for Pediatric Studies' under the pediatric exclusivity program. This letter can either be sent in response to an applicant's proposed pediatric study request (PPSR) or as an FDA initiated letter.
Notes:	Link this letter to any applicable Proposed Pediatric Study Request (PPSR) or amended PPSR (IND or NDA) and to the initial submission (N-000) for all other NDAs for the active moiety belonging to the same applicant, including any applications where the active moiety is part of a combination product.

Version: 03/21/2017

END OF DOCUMENT INFORMATION PAGE

The letter begins on the next page.



NDA #####; may list IND only if there is no NDA

WRITTEN REQUEST

SPONSOR/APPLICANT NAME

Attention: CONTACT, TITLE

TITLE

ADDRESS

Dear CONTACT:

Reference is made to your DATE Proposed Pediatric Study Request for DRUG PRODUCT(S).

BACKGROUND:

This/These study/studies investigate the potential use of ACTIVE MOIETY in the treatment of PATIENT POPULATION AND INDICATION.

BRIEFLY DESCRIBE THE PUBLIC HEALTH BENEFIT (DISEASE PREVALENCE, LACK OF ALTERNATE THERAPIES, ETC.), INCLUDE INFORMATION ABOUT WHY EFFICACY MUST BE ESTABLISHED IN THE PEDIATRIC POPULATION OR WHY EXTRAPOLATION IS APPROPRIATE. IF STUDIES ARE NOT REQUESTED IN NEONATES, INCLUDE A STATEMENT DESCRIBING THE RATIONALE FOR NOT REQUESTING STUDIES IN NEONATES.

To obtain needed pediatric information on ACTIVE MOIETY, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, that you submit information from the studies described below.

COMPLETE AND INCLUDE ALL APPROPRIATE SECTIONS

- *Nonclinical study(ies):*

UNDER PROVISIONS OF THE ACT, SECTION 505A (A), NONCLINICAL STUDIES MAY BE INCLUDED IN A WRITTEN REQUEST IF NEEDED TO INFORM POTENTIAL SAFETY CONCERNS FOR USE OF THE DRUG IN PEDIATRIC POPULATIONS. SELECT ONE OF THE FOLLOWING STATEMENTS:

Based on review of the available nonclinical toxicology, no additional animal studies are required at this time to support the clinical studies described in this written request.

Based on review of the available nonclinical toxicology, the following study/studies must be conducted prior to the start of the clinical study/studies described in this written request. ADD STUDY REQUIREMENT (E.G., JUVENILE ANIMAL TOXICITY STUDY, OR OTHER RELEVANT STUDY TYPE). SPECIFY IF, FOR A GIVEN AGE GROUP, NONCLINICAL TRIALS NEED TO BE COMPLETED BEFORE CLINICAL STUDIES ARE INITIATED.

- *Clinical studies:*

LIST SPECIFIC STUDIES REQUIRED AND DEFINE STUDY DESIGN (E.G., DOUBLE-BLIND, RANDOMIZED, PARALLEL GROUP, SAFETY, AND/OR PK).

Study 1:

Study 2:

SELECT FROM THE FOLLOWING TEMPLATE LANGUAGE TO DESCRIBE THE USE OF EXTRAPOLATION FOR EFFICACY.

- Efficacy in INSERT PEDIATRIC AGE COHORT will be supported by INSERT RATIONALE OR REQUIREMENTS FOR EXTRAPOLATION AND THE AGE GROUP FROM WHICH EXTRAPOLATION WILL OCCUR
- Efficacy in INSERT PEDIATRIC AGE COHORT cannot be extrapolated and will be determined by the studies outlined in the WR.

SELECT THE FOLLOWING TEMPLATE LANGUAGE WHEN APPROPRIATE TO DEFINE IMPLEMENTATION TIMELINE(S) FOR STUDY(IES) DESCRIBED IN THE WRITTEN REQUEST.

- The nonclinical studies must be completed prior to the implementation of clinical studies.
- The nonclinical studies must be completed and results reported to the Agency prior to the initiation of clinical studies.
- The PHARMACOKINETIC AND/OR PHARMACODYNAMIC AS APPROPRIATE study(ies) must be completed before the efficacy trial(s) to inform dosing.
- The PHARMACOKINETIC AND/OR PHARMACODYNAMIC AS APPROPRIATE study(ies) must be completed before the efficacy trial(s) to inform dosing. Results of the results of the study(ies) must be reported to the Agency prior to the initiation of additional clinical studies.
- INSERT STUDY(IES) must be completed in INSERT AGE COHORT before proceeding in INSERT AGE COHORT in order to better define INSERT WHAT IS TO BE DEFINED.

- *Objective of each study:*
- *Patients to be Studied:*
 - *Age group in which study(ies) will be performed:* INDICATE SPECIFIC AGE RANGES for each study.
 - *Number of patients to be studied:* INDICATE for EACH STUDY.

Representation of Ethnic and Racial Minorities: The studies must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities. If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.

- *Study endpoints:*

INCLUDE THE FOLLOWING TEMPLATE LANGUAGE WHEN APPROPRIATE

Pharmacokinetic Endpoints:

The pharmacokinetic endpoints for INSERT STUDY # must include INSERT REQUIRED MEASUREMENTS, INSERT TIMING OF ENDPOINTS, MINIMUM FREQUENCY, POPULATION IN WHICH ENDPOINTS SHOULD BE OBTAINED, OTHER.

Pharmacokinetic/Pharmacodynamic Endpoints:

The pharmacokinetic and pharmacodynamic endpoints for INSERT STUDY # must include INSERT REQUIRED MEASUREMENTS, INSERT TIMING OF ENDPOINTS, MINIMUM FREQUENCY, POPULATION IN WHICH ENDPOINTS SHOULD BE OBTAINED, OTHER.

Efficacy Endpoints;

The primary efficacy endpoint will be INSERT PRIMARY ENDPOINT and must be assessed by INSERT EXPECTATIONS FOR METHOD OF ASSESSMENT, MAY INCLUDE SCALES VALIDATED FOR PEDIATRIC POPULATION OF INTEREST

Important secondary endpoints must include INSERT IMPORTANT SECONDARY ENDPOINTS and must be assessed by INSERT METHOD OF ASSESSMENT, MAY INCLUDE SCALES VALIDATED FOR PEDIATRIC POPULATION OF INTEREST

Measures of compliance must include INSERT REQUIRED COMPLIANCE MEASURES

Safety Endpoints:

- Safety outcomes must include INSERT AS APPROPRIATE: ADVERSE EVENTS, TOLERABILITY, VITAL SIGNS, LABORATORY PARAMETERS, GROWTH PARAMETERS AND DEVELOPMENT BASED ON KNOWN AE PROFILE OF PRODUCT AND ANY SPECIFIC PEDIATRIC SAFETY CONCERNS.
- The following adverse events must be actively monitored: INSERT ADVERSE EVENTS REQUIRING ACTIVE MONITORING AND METHOD FREQUENCY AND DURATION OF MONITORING. All adverse events must be monitored until symptom resolution or until the condition stabilizes.
- The following adverse events must be captured when spontaneously reported: INSERT AE'S TO BE RECORDED WHEN SPONTANEOUSLY REPORTED
- A Data Monitoring Committee (DMC) must be included because [INSERT REASON(S) FROM LIST BELOW. See Guidance: Establishment and Operation of Clinical Trial Data Monitoring Committees <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126578.pdf>
 - findings INSERT FAVORABLE RESULT, UNFAVORABLE RESULT, OR "OF FUTILITY" at an interim analysis may ethically require termination of the study before its planned completion;
 - of INSERT PARTICULAR SAFETY CONCERN,
 - of the possibility of serious toxicity with MOIETY OR TREATMENT
 - the study is being performed in children, a potentially fragile population
 - the study is being performed in a population at elevated risk of death or other serious outcomes,
 - the study is large, of long duration, and multi-center.

- *Known Drug Safety concerns and monitoring:*
- *Extraordinary results:* In the course of conducting these studies, you may discover evidence to indicate that there are unexpected safety concerns, unexpected findings of benefit in a smaller sample size, or other unexpected results. In the event of such findings, there may be a need to deviate from the requirements of this Written Request. If you believe this is the case, you must contact the Agency to seek an amendment. It is solely within the Agency's discretion to decide whether it is appropriate to issue an amendment.
- *Drug information:*

- *dosage form*
- *route of administration*
- *regimen*

Use an age-appropriate formulation in the study(ies) described above. If an age-appropriate formulation is not currently available, you must develop and test an age-appropriate formulation and, if it is found safe and effective in the studied pediatric population(s), you must seek marketing approval for that age-appropriate formulation.

In accordance with section 505A(e)(2), if

- 1) you develop an age-appropriate formulation that is found to be safe and effective in the pediatric population(s) studied (i.e., receives approval);
- 2) the Agency grants pediatric exclusivity, including publishing the exclusivity determination notice required under section 505A(e)(1) of the Act; and
- 3) you have not marketed the formulation within one year after the Agency publishes such notice,

the Agency will publish a second notice indicating you have not marketed the new pediatric formulation.

If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age-appropriate formulation that can be prepared by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients. Under these circumstances, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable, age-appropriate formulation, then you must submit instructions for preparing an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using such a formulation, the following information must be provided for inclusion in the product labeling upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step preparation instructions; packaging and storage requirements; and formulation stability information.

Bioavailability of any formulation used in the studies must be characterized, and as needed, a relative bioavailability study comparing the approved drug to the age appropriate formulation may be conducted in adults.

- *Statistical information, including power of study(ies) and statistical assessments:*

- *Labeling that may result from the study(ies):* You must submit proposed pediatric labeling to incorporate the findings of the study(ies). Under section 505A(j) of the Act, regardless of whether the study(ies) demonstrate that **ACTIVE MOIETY** is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the study(ies). Under section 505A(k)(2) of the Act, you must distribute to physicians and other health care providers at least annually (or more frequently if FDA determines that it would be beneficial to the public health), information regarding such labeling changes that are approved as a result of the study(ies).
- *Format and types of reports to be submitted:* You must submit full study reports (which have not been previously submitted to the Agency) that address the issues outlined in this request, with full analysis, assessment, and interpretation. In addition, the reports must include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study(ies) should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity, you should use one of the following designations: Hispanic/Latino or Not Hispanic/Latino. If you choose to use other categories, you should obtain agency agreement. **INCLUDE OTHER INFORMATION AS APPROPRIATE**

Under section 505A(d)(2)(B) of the Act, when you submit the study reports, you must submit all postmarketing adverse event reports regarding this drug that are available to you at that time. All post-market reports that would be reportable under section 21 CFR 314.80 should include adverse events occurring in an adult or a pediatric patient. In general, the format of the post-market adverse event report should follow the model for a periodic safety update report described in the Guidance for Industry E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs and the Guidance addendum. You are encouraged to contact the reviewing Division for further guidance.

Although not currently required, we request that study data be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document “Study Data Specifications,” which is posted on the <https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM312964.pdf> and referenced in the FDA Guidance for Industry, *Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* at <https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm333969.pdf>.

- *Timeframe for submitting reports of the study(ies):* Reports of the above studies must be submitted to the Agency on or before **INSERT DATE**. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study reports are submitted to make a pediatric exclusivity

determination. Therefore, to ensure that a particular patent or exclusivity is eligible for pediatric exclusivity to attach, you are advised to submit the reports of the studies at least 15 months (9 months plus 6 months/180 days for determination) before such patent or exclusivity is otherwise due to expire.

- *Response to Written Request:* Under section 505A(d)(2)(A)(i), within 180 days of receipt of this Written Request you must notify the Agency whether or not you agree to the Written Request. If you agree to the request, you must indicate when the pediatric studies will be initiated. If you do not agree to the request, you must indicate why you are declining to conduct the study(ies). If you decline on the grounds that it is not possible to develop the appropriate pediatric formulation, you must submit to us the reasons it cannot be developed.

Furthermore, if you agree to conduct the study(ies), but have not submitted the study reports on or before the date specified in the Written Request, the Agency may utilize the process discussed in section 505A(n) of the Act.

Submit protocols for the above study(ies) to an investigational new drug application (IND) and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY**" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the study(ies) must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF PEDIATRIC STUDY REPORTS - PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED**" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission to the Director, Office of Generic Drugs, CDER, FDA, Document Control Room, Metro Park North VII, 7620 Standish Place, Rockville, MD 20855-2773. If you wish to fax it, the fax number is 240-276-9327.

In accordance with section 505A(k)(1) of the Act, *Dissemination of Pediatric Information*, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following circumstances:

1. the type of response to the Written Request (i.e. complete or partial response);
2. the status of the application (i.e. withdrawn after the supplement has been filed or pending);
3. the action taken (i.e. approval, complete response); or
4. the exclusivity determination (i.e. granted or denied).

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049872>

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

Please note that, if your trial is considered an "applicable clinical trial" under section 402(j)(1)(A)(i) of the Public Health Service Act (PHS Act), you are required to comply with the provisions of section 402(j) of the PHS Act with regard to registration of your trial and submission of trial results. Additional information on submission of such information can be found at www.ClinicalTrials.gov.

If you have any questions, call **NAME**, Regulatory Project Manager, at **PHONE NUMBER**.

Sincerely,

{See appended electronic signature page}

OFFICE DIRECTOR

Director

Office of Drug Evaluation **XX**

Center for Drug Evaluation and Research