NDA 206829

WRITTEN REQUEST – AMENDMENT 1

Cubist Pharmaceuticals, LLC
c/o Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc.
Attention: Casey Raudenbush, MSN
Senior Director, Global Regulatory Affairs
351 North Sumneytown Pike
P.O. Box 1000, UG2D-68
North Wales, PA 19454-2505

Dear Casey Raudenbush:

Please refer to your correspondence dated July 26, 2023, and amendment dated August 4, 2023, requesting changes to FDA's February 8, 2022, Written Request for pediatric studies for Zerbaxa (ceftolozane and tazobactam).

We have reviewed your proposed changes and are amending the Written Request. All other terms stated in our Written Request issued on February 8, 2022, and as amended on July 26 and August 4, 2023, remain the same. (Text added is underlined. Text deleted is strikethrough.)

> *Timeframe for submitting reports of the study:* Reports of the above study(ies) must be submitted to the Agency on or before ~~November 30, 2023~~ June 30, 2026. 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 study(ies) at least 15 months (9 months plus 6 months/180 days for determination) before such patent or exclusivity is otherwise due to expire.

For ease of reference, a complete copy of the Written Request, as amended, is attached to this letter.

Reports of the studies that meet the terms of the Written Request dated February 8, 2022, as amended by this letter and by previous amendments, dated July 26 and August 4, 2023, must be submitted to the Agency on or before June 30, 2026, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

Submit reports of the studies as a new drug application (NDA) / supplement to an approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, 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.

In accordance with section 505A(k)(1) of the Act, 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:

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- the status of the application (i.e., withdrawn after the supplement has been filed or pending);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

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website.[1]

If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to your application. Clearly mark submissions of proposed changes to this request **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. We will notify you in writing if we agree to any changes to this Written Request.

If you have any questions, call Deborah Kim, PharmD, RAC, Senior Regulatory Project Manager, at (301) 796-9053.

Sincerely,

{See appended electronic signature page}

John Farley, MD, MPH
Director
Office of Infectious Diseases
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE:

- Complete Copy of Pediatric Written Request – Amendment 1

[1] https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm316937.htm

NDA 206829

WRITTEN REQUEST – AMENDMENT 1

Cubist Pharmaceuticals, LLC
c/o Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc.
Attention: Casey Raudenbush, MSN
Director, Global Regulatory Affairs
351 North Sumneytown Pike
P.O. Box 1000, UG2D-68
North Wales, PA 19454-2505

Dear Casey Raudenbush:

Please refer to your correspondence dated July 26, 2023, and amendment dated August 4, 2023, requesting changes to FDA's February 8, 2022, Written Request for pediatric studies for Zerbaxa (ceftolozane and tazobactam).

This study investigates the potential use of ceftolozane and tazobactam in the treatment of nosocomial pneumonia (NP) in pediatric patients from birth to less than 18 years of age.

BACKGROUND:

Nosocomial pneumonia (NP) is a type of pneumonia that develops at least 48 hours after admission to a hospital and was not present at the time of hospital admission. Hospital-acquired bacterial pneumonia (HABP) and ventilator-associated bacterial pneumonia (VABP) are subcategories of NP and are closely related infections of the lung parenchyma involving similar pathogens. HABP is defined as a bacterial pneumonia that begins more than 48 hours after hospital admission or within 7 days after hospital discharge. VABP is a bacterial lung infection that develops in a patient who has been intubated for more than 48 hours. HABP and VABP are common nosocomial infections in both adult and pediatric populations in the US, accounting for 10-12% of pediatric patient admissions to the intensive care unit (ICU) and are associated with increased length of hospital stay, and mortality rates in the range of 8-71%.

Although NP can be caused by a variety of pathogens, gram-negative bacilli are the predominant causative pathogens of NP and include *Escherichia coli (E. coli)*, *Klebsiella pneumoniae (K. pneumoniae)* and *Pseudomonas aeruginosa (P. aeruginosa)*. In pediatric patients, *P. aeruginosa* is considered the leading cause of NP. NP due to multidrug resistant (MDR) pathogens are associated with prolonged hospitalization and increased risk for mortality.

Ceftolozane/tazobactam is a combination of the cephalosporin, ceftolozane, and the beta-lactamase inhibitor (BLI), tazobactam. It has activity against most common gram-negative organisms, including strains of multidrug-resistant (MDR) *P. aeruginosa* and ESBL-producing Enterobacteriaceae. It was originally approved on December 10, 2014, for the treatment of complicated urinary tract infections (cUTI) including pyelonephritis, and complicated intra-abdominal infections (cIAI) (in conjunction with metronidazole).

Ceftolozane/tazobactam also received approval for the treatment of HABP and VABP in adults on June 3, 2019. Ceftolozane/tazobactam could provide an additional treatment option for pediatric NP patients. Pediatric studies in cUTI and cIAI are not included in this WR because full pediatric assessments have been submitted to FDA and are under review. Studies for the use of this product in the treatment of pulmonary exacerbations in patients with CF have not been included in this WR, but this remains an area of interest and the WR would need to be amended in the future if FDA determines that studies in CF are feasible.

The Division of Anti-infectives (DAI) has determined that the course of NP (HABP/VABP) in pediatric patients is sufficiently similar to HABP/VABP in adults to allow extrapolation of efficacy from the adult clinical trials to pediatric patients. Pediatric patients with NP, with exposures equivalent to the effective adult ceftolozane/tazobactam exposures, should have treatment responses similar to adults. Although there are some safety and pharmacokinetic (PK) data in pediatric patients from the completed studies in cIAI and cUTI, additional safety and PK data pertaining to treatment of NP in pediatric patients will be needed to optimize dosing.

To obtain needed pediatric information on ceftolozane/ tazobactam, 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 study(ies) described below.

- *Nonclinical study(ies)*:
  Based on review of the available nonclinical toxicology of ceftolozane/tazobactam, no additional animal studies are required at this time to support the clinical study described in this Written Request.

- *Clinical study:*
  An open-label, non-comparative, multicenter clinical study to evaluate the safety, tolerability, and pharmacokinetics of ceftolozane/tazobactam in pediatric participants from birth (>32 weeks gestational age and ≥7 days postnatal) to <18 years of age with nosocomial pneumonia.

- *Study Objectives:*
  The primary objective will be to evaluate the safety and tolerability of ceftolozane/tazobactam for all participants, as measured by:

- AEs, including any AEs, any SAEs, any deaths, changes in laboratory parameters, changes in vital signs,

- AEs leading to discontinuation of study intervention

Key secondary objectives will be to evaluate the PK of multiple doses of ceftolozane/tazobactam for each age group and/or dose level, measured by:

- Plasma concentrations for ceftolozane and tazobactam measured at time points as agreed upon with FDA in the study protocol

- Steady state plasma area under the concentration-time curve (AUCss), maximum observed concentration during a dosage interval (Cmax), elimination half-life (t1/2), volume of distribution (Vd), and clearance (CL) for ceftolozane and tazobactam

- *Patients to be Studied:*

  - *Age groups to be studied:* Pediatric patients from birth (>32 weeks gestational age and ≥7 days postnatal) to <18 years of age with NP must be enrolled in the study into 5 age groups: 12 to <18 years, 7 to <12 years, 2 to <7 years, 3 months to <2 years, and birth (>32 weeks gestational age and ≥7 days postnatal) to <3 months.

  - *Representation of Ethnic and Racial Minorities:* The study 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.

  - *Number of patients to be studied:* Approximately 40 patients should be enrolled, with a minimum of 6 PK evaluable patients in each age cohort must complete the study.

- *Study endpoints:*

  - Safety Endpoints/Monitoring*:* The protocol must include a plan for monitoring and reporting of the following safety endpoints: adverse events (AEs, serious AEs, AEs leading to discontinuation of study intervention, deaths, changes in laboratory parameters, changes in vital signs).

    The protocol must also include a plan for monitoring of all adverse until resolution or stabilization of the AE.

- Pharmacokinetic/Pharmacodynamic endpoints: ceftolozane and tazobactam PK parameters including plasma concentrations at each protocol-defined sampling timepoint, steady state plasma AUCss, Cmax, t1/2, Vd, and CL, to identify doses for all pediatric age ranges

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

  - Plasma concentration data and PK parameters must be summarized by descriptive statistics.

  - The study must include an adequate number of subjects to characterize pharmacokinetics to support dose selection. Additionally, the study must be prospectively powered to achieve a 95% CI within 60% and 140% of the point estimate of the geometric mean estimates of clearance for ceftolozane-tazobactam in each pediatric age group. Final selection of the sample size for each age group must account for potential sources of variability, including inter-subject and intra-subject variability. As study data are evaluated, the sample size must be increased as necessary to achieve the statistical power as stated above for adequate characterization of pharmacokinetics across the intended age range.

The following information pertains to all clinical studies in the Written Request.

- *Extraordinary results:* In the course of conducting this study, 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*: powder concentrate for infusion [same formulation as adult formulation]

  - *Route of Administration*: intravenous infusion

  - *Regimen*: one-hour infusion every 8 hours to be determined for each pediatric age range

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 study(ies) 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 study(ies) must be characterized, and as needed, a relative bioavailability study comparing the approved drug to the age-appropriate formulation may be conducted in adults.

- *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 ceftolozane and tazobactam 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.

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.[1] You are encouraged to contact the reviewing Division for further guidance.

For studies started after December 17, 2017 , study data must 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 FDA.gov[2] and referenced in the guidance for industry *Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*.

- *Timeframe for submitting reports of the study:* Reports of the above study(ies) must be submitted to the Agency on or before June 30, 2026. 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

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm
[2] https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM312964.pdf

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 study(ies) 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 study(ies) 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 study(ies). 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.

In accordance with section 505A(k)(1) of the FD&C Act, *Dissemination of Pediatric Information*, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric study(ies) 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.[3]

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 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 on the Clinical Trials website.[4]

If you have any questions, call Deborah Kim, PharmD, RAC, Senior Regulatory Project Manager, at (301) 796-9053.

Sincerely,

{See appended electronic signature page}

John Farley, MD, MPH
Director
Office of Infectious Diseases
Office of New Drugs
Center for Drug Evaluation and Research

[3] https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm316937.htm
[4] www.ClinicalTrials.gov

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JOHN J FARLEY
09/08/2023 01:09:32 PM