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April 15, 2016

Sumathi Nambiar, M.D., M.P.H.
Director, Division of Anti-Infective Products
Center for Drug Evaluation and Research, HFD-520
Food and Drug Administration

NDA 021572: CUBICIN® (daptomycin for injection)
RESPONSE TO PREA NON-COMPLIANCE LETTER
AND DENIAL OF DEFERRAL EXTENSION REQUEST

Dear Dr. Nambiar:

Reference is made to the FDA's letter, dated March 3, 2016, notifying Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. ("Merck" or the "Sponsor"), of its non-compliance with a postmarketing requirement ("PMR") under the Pediatric Research Equity Act ("PREA"). Reference is also made to the FDA's letter of March 2, 2016 denying Merck's October 7, 2015 request for a deferral extension related to that same PMR.

This submission contains the following:

- Response to FDA's non-compliance with a PMR under PREA, which can be found in Module 1.9.6
- References cited within the response letter

This submission is being submitted in accordance with the current FDA Guidance Documents for the electronic common technical document. This submission is being transmitted through the FDA's electronic submission gateway. The Sponsor has taken precautions to ensure that the contents are free of computer viruses (McAfee Agent, McAfee, Inc.), and authorizes the use of anti-virus software, as appropriate.

We consider the information included in this submission to be a confidential matter, and request that the FDA not make its content public without first obtaining the written permission of Cubist Pharmaceuticals, LLC and its parent company, Merck.

For further information or questions, please contact me by phone at 267-305-1644 or e-mail sandra_wood2@merck.com. In my absence questions concerning the content of this submission should be directed to Sandip Roy, Ph.D. (732-594-4211 or e-mail sandip.roy1@merck.com).

Sincerely yours,
Sandra Lynn Wood, Ph.D.
Director, Global Regulatory Affairs,
Merck Sharp & Dohme Corp., as
agent for Cubist Pharmaceuticals
LLC

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Further references are made to the following submissions:

- Submission Sequence 00109, the Final Study Report for the multiple dose safety and efficacy study in children aged 1 to 17 years being treated for complicated skin and skin structure infections (cSSSI) [DAP-PEDS-07-03] to IND 57,693 (Sequence No. 165) with a cross-reference letter to NDA 21-572 (Sequence No. 109).
- Submission Sequence 00116, a Pediatric Deferral Extension Request submitted to the Agency on October 7, 2015.

The purpose of this letter is to affirm Merck's continued commitment to fulfill all outstanding PREA PMRs for CUBICIN and to respond specifically to both FDA letters referenced above.

CUBICIN was approved by FDA on September 12, 2003. PREA was enacted several months later on December 3, 2003. On August 18, 2005, FDA issued a post-marketing study commitment for CUBICIN, which was subsequently re-issued, on February 11, 2015, as PMR 2864-1:

- *Conduct a multi-center, evaluator blinded, randomized comparator study designed to assess the safety, efficacy, and PK of three age dependent doses of IV daptomycin administered for up to 14 days in pediatric patients aged 1 to 17 years, inclusive with cSSSI caused by Gram positive pathogens.*
- Final Report Submission Deadline: August 31, 2015

On June 2, 2015, nearly three months in advance of the August 31, 2015 submission deadline, Merck submitted the final study report for PMR 2864-1 (Merck Study Number: DAP-PEDS-07-03). It did not submit labeling at that time because it planned to submit the labeling associated with PMR 2864-1 along with an efficacy supplement related to another PREA PMR for CUBICIN, a *Staphylococcus aureus* bacteremia ("SAB") study (DAP-PEDBAC-11-02/PMR 804-7)], in the second half of 2016.

Merck believed that the combined submission of the labeling for the two PMRs was justified scientifically for two reasons. First, the pediatric dosing for cSSSI and SAB differ, with higher doses currently under evaluation for the SAB indication (7-12 mg/kg for up to 42 days) as compared to the cSSSI indication (5-10 mg/kg/day for up to 14 days). As a result, labeling focused solely on supporting cSSSI dosing recommendations might not sufficiently address issues related to appropriate therapy of pediatric cSSSI where SAB is suspected or confirmed. Second, pediatric patients with cSSSI are at increased risk for developing SAB. For example, in a cohort of 80 pediatric patients with complicated skin and soft tissue structure infections [SSTI] (mean age 5.8 years) who had a blood culture, bacteremia was detected in 10 patients (12.5%) [3]. Meanwhile, current pediatric guidelines for cSSSI differ regarding the choice of therapy and dosing regimens based on the presence or absence of bacteremia [1-2], potentially leading to confusion among health-care providers. Hence, Merck believed, pediatric dosing recommendations in CUBICIN labeling focused *solely* on the cSSSI indication could prove challenging for health-care providers treating pediatric patients who have both cSSSI *and* bacteremia, or in patients with severe cSSSI where the results of blood cultures are unknown (or pending).

On October 1, 2015, Merck received an e-mail from the FDA requesting a brief telephone call on that date regarding the final study report for PMR 2864-1 (DAP-PEDS-07-03). During the resulting call, the FDA acknowledged Merck's timely submission of the final study report for PMR 2864-1, but stated that labeling must also be submitted to fulfill the PREA PMR. In response, Merck explained its rationale for submitting the labeling for the two PMRs together in the second half of 2016. The FDA suggested that Merck submit a request for a deferral extension for PMR 2864-1 that explained this rationale and set a date for submission of the labeling for both PMRs. Merck submitted the deferral extension request on October 7, 2015.

In a letter dated March 2, 2016, FDA denied Merck's October 7, 2015 request for a deferral extension. FDA rejected Merck's scientific rationale for submitting the labeling for cSSSI and SAB together, stating that Merck's plan to do so did not "adequately justify a delay" in submitting the cSSSI labeling alone. The next day, March 3, 2016, FDA sent Merck a letter notifying the company that it was non-compliant with PREA because it had not submitted

labeling for PMR 2864-1. In this same letter, FDA reiterated its rejection of Merck's request for a deferral, emphasizing that Merck's request "does not qualify for an extension."

Merck is committed to complying in a timely manner and in full with its PMR obligations, including those under PREA, and therefore, proposes to submit labeling for PMR 2864-1 no later than June 30, 2016. The supplement for the SAB study will follow by its due date, March 15, 2017.

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Sandra Lynn Wood, Ph.D.
Director, Global Regulatory Affairs,
Merck Sharp & Dohme Corp., as
agent for Cubist Pharmaceuticals
LLC

cc: Joseph G. Toerner, M.D., M.P.H., Deputy Director for Safety; Division of Pediatric & Maternal Health Office of New Drugs

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