PACIRA
PHARMACEUTICALS, INC.

November 19, 2020

Rigoberto Roca, MD
Director, Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Food and Drug Administration
Center for Drug Evaluation and Research
5901-B Ammendale Road
Beltsville, MD 20705-1266

Attention: **Mavis Y. Darkwah, Pharm.D.**
Regulatory Health Project Manager, DAAP

Subject: **NDA 022496**
EXPAREL® (bupivacaine liposome injectable suspension)
Sequence No. 0239
Response To PREA Non-Compliance Letter

Dear Dr. Roca,

We refer to your Notification of Non-Compliance with the Pediatric Research Equity Act ("PREA"), dated November 6, 2020, in which you notified Pacira Pharmaceuticals, Inc. ("Pacira"), a wholly owned subsidiary of Pacira BioSciences, Inc., that Pacira was not in compliance with Postmarketing Requirement 3372-1 (PMR 3372-1) for a multicenter, randomized, double-blind, parallel-group, bupivacaine-controlled study to evaluate the safety and pharmacokinetic profile of EXPAREL as an interscalene brachial plexus nerve block to produce postsurgical analgesia in adolescent patients 12 to less than 17 years of age. Specifically, you stated that we did not submit either a pediatric assessment or a request for a deferral extension for this PMR. Considering the history of open and transparent communications that we have had with the Division of Anesthesiology, Addiction Medicine, and Pain Medicine ("DAAP") regarding this PMR, we disagree with the issuance of this letter and respectfully request that DAAP retract it.

Following the approval of NDA supplement 022496/S-009 on April 6, 2018, which was associated with PMR 3371-1 for a study in pediatric patients 12 to less than 17 years of age and PMR 3371-2 for a study in pediatric patients 6 to less than 12 years of age, we discussed both PMRs with DAAP during our April 23, 2018 Type C meeting and emphasized the difficulty we foresaw in being able to conduct pediatric studies using EXPAREL as an interscalene brachial plexus nerve block. As recorded in the Division's May 11, 2018 minutes to that meeting, DAAP responded that it "would accept a feasibility argument for not conducting a pediatric brachial plexus block study as long as it was well supported."

Following the April 23, 2018 discussion, in our submission on July 18, 2018 (IND 069198, Serial Number 0238), we explained more fully our rationale for why we did not believe that it would be feasible to conduct pediatric studies for interscalene brachial plexus nerve block in pediatric subjects aged 6 to less than 17 years. In DAAP's information request of November 9, 2018, the Division concurred that a randomized, double-blind study of EXPAREL via interscalene nerve block might be difficult to conduct in subjects aged 12 to less than 17 years old as well as in subjects aged 6 to less than 12 years old. The Division also noted that the brachial plexus block

was gaining popularity in pediatric subjects, and that we might be able to formulate a justification to support the extrapolation of efficacy from adults to these adolescent patients without the need to conduct a clinical study. Consequently, DAAP requested that we provide a justification for an EXPAREL dose via interscalene nerve block in patients 12 to less than 17 years of age and (b) (4) .

In response to the Division's information request, we submitted a rationale for the use of EXPAREL at a dose of (b) (4), up to a maximum of (b) (4), via interscalene brachial plexus nerve block in patients 12 to less than 17 years of age on December 20, 2018 (NDA 022496; Sequence Number 0206). Subsequently, in the Division's General Advice letter of January 23, 2019, DAAP requested that all PK and safety data from Study 402-C-120 (Study 120) be provided before any additional discussions could take place. Because the clinical study report for Study 120 was still in development at the time of this General Advice letter, we were not able to address the request immediately, but subsequently we submitted the clinical study report for Study 120 upon its completion on July 17, 2019 (NDA 022496, Sequence Number 0211)

Following the submission of the clinical study report for Study 120, we inquired during our Type B meeting of August 28, 2019 regarding the next steps with respect to PMR 3372-1. As stated in DAAP's September 24, 2019 minutes from that meeting:

> "*The Sponsor asked if the Division had any questions or concerns regarding the unfeasibility of brachial plexus nerve block in pediatrics. The Division had no comment. The Sponsor asked if providing a satisfactory rationale for dosing with* (b) (4) *would be sufficient* (b) (4) *from a procedural standpoint to which the Division stated that comments are being finalized regarding the dose and would be sent to the Sponsor when completed.*"

Despite DAAP's indication in August 2019 that comments were being finalized regarding the dose, we did not receive any comments for more than a year. Finally, in an August 25, 2020 e-mail correspondence from Dr. Hetal Pansuria of Pacira to Dr. Mavis Darkwah of DAAP, Dr. Pansuria inquired how Pacira should move forward with PMR 3372-1, considering the upcoming submission due date of August 31, 2020. After an exchange of e-mails between Dr. Pansuria and Dr. Darkwah, Dr. Darkwah finally indicated in a September 9, 2020 e-mail that the dosing proposal that Pacira had submitted on December 20, 2018 was still under review and requested that we submit an extension request for PMR 3372-1. Pacira submitted the extension request for PMR 3372-1 to the subject NDA on October 2, 2020 (Sequence Number 0233). On October 15, 2020, Pacira received a General Advice letter stating that the Division did not agree to our proposed dose for the use of EXPAREL as an interscalene brachial plexus block in patients 12 to less than 17 years of age.

In summary, Pacira interpreted DAAP's agreement in its November 9, 2018 information request that it would be difficult to conduct a brachial plexus study for EXPAREL in pediatric patients, and DAAP's request that we submit a proposal for a dose without the need to conduct a clinical study, as agreement that Pacira's submission of such a proposal would be in lieu of submitting a proposal for a clinical study, at least for the duration of time that the proposal would be under review. We also understood DAAP's request for a proposal to indicate that, if the Division ultimately did not agree to our proposal for a dose in subjects aged 12 to less than 17 years old

without the need for a clinical study, the Division would inform us how we should proceed to address PMR 3372-1.

We note that the time between our submission of a proposed dose (December 20, 2018) and DAAP's General Advice letter informing us that our proposal was not acceptable (October 15, 2020) was almost two years. With our proposal still under review by DAAP at the time the PMR milestone came due, it would have been unfeasible to meet the submission due date without the Division's input, and we did not receive that input until after the milestone had passed. In addition, we note that when Dr. Pansuria inquired on August 25, 2020 of how we should progress with responding to the PMR due date of August 31, 2020, there was no urgency communicated to us by the Division that time was very short and that if we did not submit an extension request prior to August 31, 2020, a Notification of Non-Compliance with PREA would be issued.

Therefore, Pacira finds the issuance of this Notification of Non-Compliance with PREA to be unwarranted, given that we have been proactive, transparent and responsive throughout the course of discussions regarding PMR 3372-1. We respectfully request that DAAP retract this Notification and grant Pacira's deferral extension request submitted for PMR 3372-1 on October 2, 2020 (Sequence Number 0233). We look forward to working with the Division to further evaluate how best to address PMR 3372-1 in light of the issues discussed herein.

As requested in your November 6, 2020 letter, a cross-reference letter to this submission is being submitted to IND 069198 (Serial No. 0312).

This submission is being provided in eCTD format. All files have been scanned using Kaspersky Endpoint Security 10 for Windows, Version 10.2.6.3733, and appear to be virus-free.

If you have any questions or concerns regarding the submission, please do not hesitate to contact me via phone at (973) 254-4310, or via email at michael.rozycki@pacira.com. In the event of my absence, please contact Dr. Hetal Pansuria, Senior Director, Regulatory Affairs, at (973) 254-4349 or via email at hetal.pansuria@pacira.com.

Sincerely,

Michael Rozycki

Digitally signed by Michael Rozycki
DN: cn=Michael Rozycki, o=Regulatory Affairs, ou=Clinical Regulatory, email=michael.rozycki@pacira.com, c=US
Date: 2020.11.19 09:57:37 -05'00'

Michael D. Rozycki, Ph.D.
Senior Vice President, Regulatory Affairs
Pacira BioSciences, Inc.

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Anti-Virus Program	Symantec Endpoint Protection Edition
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