CORPORATE HEADQUARTERS
Eagle Pharmaceuticals, Inc.
50 Tice Boulevard, Suite 315
Woodcliff Lake, NJ 07677
Tel: +1-201-326-5300

REGIONAL OFFICE
Acacia Pharma Inc
8440 Allison Pointe Blvd
Indianapolis, IN 46250
Tel: +1-317-505-1280

RESPONSE TO PREA NON-COMPLIANCE LETTER
DEFERRAL EXTENSION REQUESTED

May 29, 2025

Leah Crisafi, MD, FASA
Director, Division of Anesthesiology, Addiction Medicine, and Pain Medicine
Office of Drug Evaluation II
Food and Drug Administration
Center for Drug Evaluation and Research
5901-B Ammendale Road
Beltsville, MD 20705-1266
USA

Re: NDA 212295

Sequence No.: 0214

BYFAVO® (remimazolam) for injection (CB-07-01; CNS 7056)
Indication: the induction and maintenance of procedural sedation in adults undergoing procedures lasting 30 minutes or less.

Sponsor: Acacia Pharma Ltd, an indirect wholly owned subsidiary of Eagle Pharmaceuticals, Inc. (the "Company")

Dear Dr. Crisafi,

Reference is made to our new drug application (NDA) for Byfavo (remimazolam) for injection, which was approved on July 2, 2020. Further reference is made to the Agency's "Notification of Non-Compliance with PREA" letter dated April 15, 2025, pertaining thereto. A copy of the April 15th communication is provided herein for reference.

We acknowledge the Agency's determination that we have not met the post marketing requirements (PMRs) of the Pediatric Research Equity Act (PREA) for this application due to not submitting our pediatric assessments for the following PMRs:

> **3889-1:** A multicenter, sequential age-group study to evaluate the pharmacokinetics, safety, and efficacy of remimazolam administered for procedural sedation in pediatric patients aged three to less than 17 years of age.
>
> **3889-4:** A juvenile animal toxicology study in a nonrodent model to characterize the effects of remimazolam on the developing central nervous system to support clinical studies in pediatric patients under three years of age.

Pursuant to 21 U.S.C. 355c(d)(1) and 355c(a)(4)(B), the Company hereby submits a response to the Agency's PREA non-compliance communication of April 15, 2025, along with a deferral extension request for PMRs 3889-1 and 3889-4.

SPONSOR RESPONSE

Background

We refer the Agency to our December 15, 2023, IND 102486 Amendment (Sequence No.: 0162), which provided a status update for the PMR's as described in approval letter for this NDA dated July 2, 2020. Additionally, more recently, our December 4, 2024, Annual Report for this NDA (Sequence No.: 0206) provided the current status of these PMR's. Lastly, we refer to our December 20, 2024, meeting request and January 17, 2025, meeting package, pertaining thereto.

As detailed in these materials, Byfavo was approved on July 2, 2020, with five PREA PMRs, including three juvenile animal toxicology studies (PMRs 3889-3, 3889-4, 3889-5) and two pediatric clinical studies (3889-1, 3889-2). Following approval, the original NDA holder, Cosmo Technologies, Ltd., transferred the NDA to Acacia Pharma Ltd. (Acacia) on July 21, 2020. Eagle Pharmaceuticals, Inc. (Eagle) acquired Acacia on June 9, 2022.

Following the initial NDA approval and transfer, Acacia initiated PMR activities with the intent to fulfill the PMRs in accordance with the approved timelines. As work progressed, however, it became increasingly apparent that extensive exploratory/pilot studies would be necessary to ensure proper study designs for the two primary clinical studies. The additional exploratory/pilot work proved challenging and required more time than initially anticipated.

When Eagle completed its acquisition of Acacia on June 9, 2022, Eagle inherited the Byfavo PMRs with the work that had been completed as of the acquisition date and milestone dates that had been established prior to its acquisition of Acacia. Acacia was already behind on the PMRs, and many of the milestone dates agreed to by Acacia had already passed at the time of Eagle's acquisition.

Following the acquisition, there was also a lengthy transition process, further complicating execution of the PMRs. This process involved the following:

- Eagle transferred Acacia's contractual obligations with the contract research organizations (CROs) previously engaged by Acacia, including informing the CROs that Eagle had assumed responsibility for all ongoing and future studies under the Acacia agreements. This introduction and transition were critical to ensure continuity and clarity in project management and expectations.
- Eagle conducted a thorough review of existing documentation and protocols to understand the current status of the studies. This included assessing any ongoing research and pending milestones.
- Given that remimazolam is a Schedule IV controlled substance, the necessary permits and documentation for international shipment to the ex-US CROs had to be secured. As part of this process, Eagle needed to complete extensive paperwork and secure approvals from the Drug Enforcement Administration (DEA). This process was time-consuming but essential to ensure that the drug product could be legally and safely transported to the CROs overseas. This process took approximately one year.
- Finally, Acacia's supply chain contractual obligations and coordination had to be transferred to Eagle. This included transfer of contracts with multiple supply chain vendors involved with manufacturing, packaging, and shipping the product.

Following the transition period, Eagle had to address additional challenges. Acacia has rights to remimazolam via a licensing agreement with Paion UK Limited (Paion). Pursuant to the license agreement, Acacia and Paion agreed to share certain PMR obligations. However, Paion's German parent filed for bankruptcy in October 2023. This halted all work on the PMR obligations that had been allocated to Paion. Paion's German parent only recently emerged from bankruptcy by virtue of being purchased by a Chinese entity in 2024. Eagle is continuing to work with Paion regarding its outstanding obligations under this agreement in furtherance of necessary PMR activities.

PMR 3889-1

The Company has continued to execute this PREA PMR in good faith despite the challenges discussed above. In addition, the study had to be put on hold to allow for formulation of a new dosing regimen, as set forth below:

- (b) (4)

During this same time period, Paion's bankruptcy led to additional changes in the study.

- (b) (4)

The Company has actively worked with FDA throughout this process. Following the acquisition and transition work discussed above, the Company has continued to develop the study protocol, including through submission of revised protocols on July 28, 2023, March 15, 2024, and August 8, 2024 and responses to related FDA Advice/Information Requests on November 8 2023, April 3, 2024, and August 23, 2024.

On December 20, 2024, the Company requested a meeting with FDA to discuss pathways to move forward that will ensure access to Byfavo for appropriate adult patients despite the Company's inability to fulfill the PREA PMRs on the original approved timelines. FDA granted the meeting on December 30, 2024. The Company submitted a briefing package on January 17, 2025, and FDA provided its preliminary comments on February 25, 2025. On February 27, 2025, the Company informed the Agency via email that it wished to cancel the meeting based on FDA's preliminary responses.

PMR 3889-4

The Company has acknowledged the need to conduct additional pilot work before it can initiate this study. Based on the division of responsibilities between the Company and Paion, this study should have been conducted by Paion, but all work toward completion of the study was halted at the time of Paion's bankruptcy. The Company is continuing to address the outstanding obligations of its license agreement with Paion and considers the study on hold until such time as the Company is able to better understand and ensure study initiation and conduct in accordance with applicable standards.

As noted above, on December 20, 2024, the Company requested a meeting with FDA to discuss its PREA PMRs and subsequently canceled the meeting based on FDA's preliminary responses provided on February 25, 2025.

DEFERRAL EXTENSION REQUEST

The Company remains committed to the continued safe and effective use of Byfavo and requests a deferral extension of required pediatric assessments to allow the continued use of Byfavo in the indicated adult population while completing required PREA PMRs on a more realistic timeline in light of current and prior study completion difficulties.

A deferral extension is warranted based on the favorable safety profile demonstrated in the limited available pediatric data for Byfavo, the continued need for treatment options in elderly and medically compromised patients, and ongoing anesthesia workforce challenges. As detailed in the briefing package of January 17, 2025:

- (b) (4)

The Company refers the Agency to its January 17, 2025 submission for detailed information on the available supporting data.

In connection with the response above discussing prior unexpected delays and ongoing difficulties, along with the above support for extending existing pediatric assessment timelines while ensuring continued availability of Byfavo as a treatment option for adult patients, the Company requests a deferral extension for the below PREA PMRs as follows:

PMR 3889-1

A multicenter, sequential age-group study to evaluate the pharmacokinetics, safety, and efficacy of remimazolam administered for procedural sedation in pediatric patients aged three to less than 17 years of age	(b) (4)

PMR 3889-4

A juvenile animal toxicology study in a nonrodent model to characterize the effects of remimazolam on the developing central nervous system to support clinical studies in pediatric patients under three years of age.	

Pursuant to PREA requirements, the Company certifies that the grounds for deferral of required pediatric assessments continue to be met, and that the Company will continue to work toward completing its PREA PMRs with due diligence at the earliest possible time.

We trust the above adequately responds to the Agency's PREA non-compliance communication of April 15, 2025, and supports our deferral extension request for PMRs 3889-1 and 3889-4. If any further information is required or if there are additional questions, please do not hesitate to contact me directly.

This submission has been provided in eCTD format in accordance with the eCTD specifications described in current guidance. An Electronic Submission Specifications form from our publishing vendor (b) (4) is provided as an attachment to this cover letter. A letter of non-repudiation authorizing (b) (4) to provide electronic signatures on behalf of the Company was submitted to FDA on December 29, 2016.

Sincerely,

Marc Stern (on behalf of Janis Picurro)

Digitally signed by Marc Stern (on behalf of Janis Picurro)
Date: 2025.05.27 18:17:01 -04'00'

Janis A. Picurro
Senior Vice President, Regulatory Affairs
Eagle Pharmaceuticals, Inc.
50 Tice Boulevard, Suite 315
Woodcliff Lake, NJ 07677
Office: 201-778-3626/Cell: 201-218-1276
Email: jpicurro@eagleus.com

Electronic Submission Specifications

This submission is compliant with FDA's Guidelines for Industry and current eCTD specifications.

All files were checked and verified to be free of viruses prior to transmission through the electronic submission gateway.

Anti-Virus Program	Microsoft Defender Antivirus
Program Version	4.18.25040.11
Virus Definition Date	01/29/2025
Submission Size	Approx. 4.7 MB