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February 19, 2021

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Food and Drug Administration
Division of Anesthesia, Analgesia, and Addiction Products
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ATTN: Mavis Darkwah, Pharm.D.
Senior Regulatory Project Manager

RESPONSE TO PREA NON-COMPLIANCE LETTER
DEFERRAL EXTENSION REQUESTED

NDA 202245/S-005: Codeine Oral Solution USP, 30 mg/5 mL
NDA 022402/S-009: Codeine Tablets USP, 15 mg, 30 mg and 60 mg

Dear Dr. Darkwah:

Reference is made to the Notification of Non-Compliance with PREA letter received by Hikma Pharmaceuticals USA Inc., on December 22, 2020 for NDAs 022402 for Codeine Sulfate Tablets and 202245 for Codeine Sulfate Oral Solution.

In that letter the FDA stated that Hikma has failed to meet the postmarketing requirements: studies 26:10 and 1784-5, for these applications. Please note that the initial draft protocol for the combined study was submitted to the IND and cross referenced to the NDAs December 2019. However, due to the focus by all to the COVID pandemic, comments regarding the protocol were not received until June 2020. The pandemic also affected the recruitment and engagement of research sites. Many research sites halted all non-essential surgeries and procedures in order to focus on COVID-19. Please note that codeine sulfate was considered an essential drug to be used for COVID patients and as this supply is limited all Hikma supply was directed to distribution for COVID patients. With those items in consideration the study was put on hold until sites and supply were available.

Even with the current use of codeine sulfate we have seen a continual decline in the use of codeine sulfate in pediatric patients. It has been noted that there has been a sharp decrease in the use of codeine in pediatrics based on the warnings by FDA and WHO. While conducting feasibility for the required codeine study in 12 – 17, several sites have responded that they no longer use the product in pediatric populations. Review of marketing data reflects this current trend. The table below shows the number of pediatric scripts for codeine from 2014-2020. (b) (4)

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The current milestone timeline for this project is noted below.

Final Protocol Submission:	02/2018
Study Completion:	05/2020
Final Report Submission:	11/2020

We are in the process of conducting a feasibility study in order to determine when sites will be starting research activities. We are also researching the feasibility of conducting this study as we have been told by several sites that participated in the previous morphine pediatric study that they do not use codeine for pediatrics under the age of 18. We respectfully request an extension to the timelines in order to adequately recruit and complete the required study.

Final Protocol Submission:	06/2021
Study Completion:	12/2021
Final Report Submission:	12/2023

Hikma Pharmaceuticals USA Inc. remains committed to working with the agency to meet its post-marketing obligations under PREA.

This correspondence is being submitted in the electronic Common Technical Document (eCTD) format. Additionally, we certify that this report is virus free via scan by Cisco.

Hikma Pharmaceuticals USA Inc. is the application holder for this product.. Correspondence concerning this submission should be directed to the undersigned by telephone at (614) 241-4108 or email at dra-columbus@hikma.com. In my absence please contact Lissa Thomas, MBA, Clinical Research Manager, Clinical Development by telephone (614-256-3481).

Regards,

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