LAW OFFICES
HYMAN, PHELPS & MCNAMARA, P.C.
700 THIRTEENTH STREET, N.W.
SUITE 1200
WASHINGTON, D.C. 20005-5929
(202) 737-5600
FACSIMILE
(202) 737-9329
www.hpm.com

KURT R. KARST

Direct Dial (202) 737-7544
KKarst@hpm.com

July 26, 2013

BY FEDERAL EXPRESS/COPY BY E-MAIL

Bob A. Rappaport, M.D.
Director
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
White Oak CDER Office Building 22
10903 New Hampshire Avenue
Silver Spring, Maryland 20993-0002

Re: NDA No. 021451 – ORAQIX (Lidocaine and Prilocaine Periodontal Gel) 2.5%/2.5%; RESPONSE TO PREA NON-COMPLIANCE LETTER

Dear Dr. Rappaport:

I am writing to you on behalf of our client, Dentsply Pharmaceutical ("Dentsply"), in response to the June 12, 2013 letter, titled "Notification of Non-Compliance with PREA," sent by the Division of Anesthesia, Analgesia, and Addiction Products ("the Division") concerning the above-referenced New Drug Application ("NDA") for ORAQIX. This response is timely submitted to FDA in accordance with Section 505B(d) of the Federal Food, Drug, and Cosmetic Act ("FDC Act"), as amended by the FDA Safety and Innovation Act of 2012.

FDA alleges in its non-compliance notification that Dentsply has "failed to meet the requirements of the Pediatric Research Equity Act (PREA) for [NDA No. 021451] because you have not submitted your pediatric assessment. . . ." To the contrary, Dentsply met the PREA requirement with the April 24, 2012 submission of a final study report to IND No. (b) (4) As such, Dentsply requests that FDA rescind the non-compliance notification and determine that Dentsply has met its statutory obligation under PREA. If FDA does not do so, and instead continues with its insistence that Dentsply submit an efficacy supplement to NDA No. 021451, along with the payment of

a $979,400 user fee, Dentsply will have no real choice but to consider its options, including reconsidering whether to continue marketing this important therapeutic product.

Please consider the following, which we believe demonstrates that Dentsply has met its statutory obligation under PREA.

FDA approved NDA No. 021451 for ORAQIX on December 19, 2003 for adults who require localized anesthesia in periodontal pockets during scaling and/or root planing. As part of the approval, FDA waived the PREA pediatric study requirement for ages 0-5 years and deferred pediatric studies for ages 6-17 years. Completion of the deferred pediatric studies and submission of the pediatric study report was initially targeted for December 19, 2008; however, due to difficulties in identifying appropriate trial sites and negotiations with FDA concerning the study protocol, Dentsply initiated the study – a study for pharmacokinetics and safety in 6-17 year old subjects in need of tooth extraction – in April 2010, and, therefore, did not complete it until August 2011.

After completing the required pediatric study, Dentsply, on April 24, 2012, submitted an 817-page final study report to IND No. (b) (4) titled "A Phase 4 Pediatric Study to Assess the Pharmacokinetics and Safety of Oraqix® Gel in Healthy Children and Adolescent Volunteers" (Study No. TP73). In March 2013, the Division demanded that Dentsply submit a Prior Approval Supplement ("PAS") to NDA No. 021451 containing the pediatric study report and proposed labeling incorporating the results of the study. After Dentsply expressed to the Division its concern that ORAQIX was never intended to be used in pediatric patients and that the PREA study was conducted merely to discharge a post-approval commitment, the Division, on March 14, 2013, once again demanded the submission of a PAS and proposed labeling changes.

On April 1, 2013, Dentsply submitted a labeling supplement to NDA No. 021451 containing the study report and proposed labeling updating the Highlights of Prescribing Information, Use in Specific Populations (Pediatric Use), and Clinical Pharmacology (Pharmacokinetics) sections of the ORAQIX labeling with information on Study No. TP73. On May 6, 2013, the Division contacted Dentsply to inform the company that it considers the April 1st supplement to be an efficacy supplement instead of a labeling supplement, and that to begin review of the submission Dentsply must pay the applicable user fee for Fiscal Year 2013 (i.e., $979,400). On May 10, 2013, Dentsply withdrew the supplement without prejudice to refiling, and the Division subsequently sent the PREA non-compliance notification.

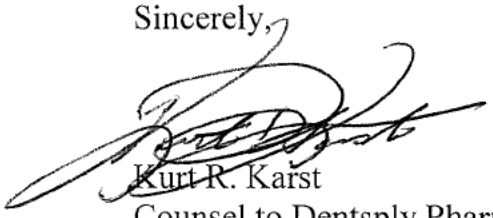
PREA, as codified at FDC Act § 505B, does not proscribe the type of submission that must be used to report to FDA the results of a pediatric assessment for a drug product. Instead, the statute generally refers to Section 505, see, e.g., FDC Act § 505B(a)(1)(A), which encompasses both NDAs (FDC Act § 505(b)) and INDs (FDC Act § 505(i)). As such, submission of a pediatric study report to an IND is not precluded.

Moreover, a supplement to an approved NDA is only appropriate where a sponsor is requesting a change in a human drug application. That is not the case here. The term "supplement" is defined in the statute to mean "a ***request*** to [FDA] to approve ***a change*** in a human drug application which has been approved." FDC Act § 735(2) (emphasis added). Even in that situation, a supplement to a human drug application containing "clinical data" seeking approval of "a change" to an approved human drug application is assessed one half of the application user fee established for the particular fiscal year in which the submission occurs. See id. at § 736(a)(1)(A). Here, however, Dentsply never intended to request a change to the ORAQIX labeling. It conducted Study No. TP73 merely to discharge the PREA requirement.

Forcing Dentsply to submit a PAS (efficacy) along with the payment of a $979,400 user fee to add to the ORAQIX labeling information from Study No. TP73 that FDA required the company to conduct does not follow from the PREA requirement. It is basically a penalty for meeting the PREA requirement, which is an illogical concept and inappropriate under these circumstances. Assuming such a supplement is approximately 850 pages in length, it amounts to a charge of a little more than $1,150 per page. Regardless, however, Dentsply questions that FDA has the explicit authority under the statute to direct the type of submission for Dentsply to report Study No. TP73. Instead, the more supported and reasonable finding would appear to be that Dentsply has met the PREA pediatric study assessment requirement by submitting the study report to IND No. (b) (4) and no further submission is necessary or warranted.

Dentsply looks forward to the Division's prompt response to this submission acknowledging that PREA non-compliance notification was issued in error and will be rescinded, and that Dentsply has met its PREA obligation.

Sincerely,



Kurt R. Karst
Counsel to Dentsply Pharmaceutical

KRK/eam

cc: Mavis Darkwah, Pharm.D.
Regulatory Project Manager, FDA

Pediatric and Maternal Health Staff, FDA

Beth A. Bodnar
RA Specialist 1, Dentsply Pharmaceutical