Docket No.: 117744-12902
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Andrew FINN *et al.*

Application No.: 13/590,094 | Confirmation No.: 5975

Filed: August 20, 2012 | Art Unit: 1619

For: ABUSE-RESISTANT MUCOADHESIVE DEVICES FOR DELIVERY OF BUPRENORPHINE | Examiner: ALAWADI, SARAH

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF NIRAJ VASISHT, PH.D. UNDER 37 CFR §1.132

I, Niraj Vasisht declare:

1. I am the Senior Vice President of Product Development and Chief Technical Officer of BioDelivery Sciences International, Inc., the owner of the instant application. I am also an inventor of the instant application.

2. I have over 20 years of experience in pharmaceutical product development and have played a significant role in the development and regulatory approval of three products. I am responsible for the development of a portfolio of products that include the innovative features claimed in the instant application, including BEMA Buprenorphine for chronic pain and BEMA Buprenorphine with Naloxone for opioid dependence. My responsibilities include pharmaceutical development and manufacturing, nonclinical and clinical development, regulatory affairs and quality assurance for these products. I received a Bachelor of Science in Chemical Engineering from the Indian Institute of Technology, Kanpur, a Master's Degree in Chemical Engineering from the University of New Hampshire and a Doctorate in Chemical Engineering from Rensselaer Polytechnic Institute. My *curriculum vitae* is attached.

RB Ex. 2003
BDSI v. RB
PHARMACEUTICALS LTD.
IPR2014-00998

3. I have read and understand the Office Action dated November 23, 2013 issued in connection with the instant application. I am also an inventor of both US 11/639,408 and PCT/US2007/016634 that correspond to, respectively, US 2007/0148097 (Finn *et al.*) and WO 2008/011194 (Vasisht *et al.*) and that were cited in the Office Action.

4. WO 2008/011194 describes transmucosal drug delivery devices comprising a mucoadhesive polymeric diffusion environment (*i.e.*, a mucoadhesive layer) and a backing layer. A drug, such as buprenorphine, is present in the mucoadhesive layer, and enhanced uptake of the drug is achieved by adjusting the pH of the mucoadhesive layer. As a result of experiments described in WO 2008/011194, we determined that enhanced buccal absorption of buprenorphine can be achieved when pH of the mucoadhesive layer is adjusted to between about 4.0 and about 6.0. In these experiments, we did not adjust the pH of the backing layer.

5. Since naloxone exhibits two pKa values – 7.3 and 10.6 – it was initially believed that when naloxone is present in the backing layer of the mucoadhesive device, it should be buffered at a very low pH, *i.e.,* 2.75, in order to minimize its absorption through the buccal route. At this pH, the drug should be completely ionized, thus reducing the transport of ionized drug through the buccal muscosa.

6. To test the effect of adjusting pH in the backing layer, we prepared and measured buccal absorption of buprenorphine and naloxone from mucoadhesive devices that contained buprenorphine in the mucoadhesive layer buffered at pH 4.75, and naloxone in the backing layer buffered at pH of 2.75. We expected the buprenorphine C_{max} of buprenorphine for our devices to be similar to that from the control Suboxone® tablets. We found that the buprenorphine C_{max} of our devices containing 0.75 mg buprenorphine/0.1875 mg naloxone was far lower than the buprenorphine C_{max} of the control Suboxone® tablet (C_{max} of 0.564 mg/mL vs. 1.28 ng/mL for the Suboxone® tablet, see Table 4, pages 22-23 of the instant application). Indeed, it was less than half of what was expected. These results demonstrated that, unexpectedly, buccal absorption of buprenorphine from the mucoadhesive layer of our devices is influenced by the pH in the backing layer.

7. With the discovery that the pH of the backing layer dramatically effects absorption of the drug in the mucoadhesive layer, through extensive experimentation we were

able to determine the pH of the backing layer that allowed us to achieve therapeutic levels of buprenorphine, while still impeding the absorption of naloxone. We arrived at a device having naloxone in the backing layer buffered at pH of between 4.0 and 4.8. The devices containing, *e.g.*, 0.75 mg buprenorphine (pH 4.75)/0.1875 mg naloxone (pH 4.25), C_{max} was 1.10 mg/mL vs. 0.853 ng/mL for the control Suboxone® tablet, and for the device containing 0.3 mg buprenorphine (pH 4.75)/0.75 mg naloxone (pH 4.25), C_{max} was 3.44 mg/mL vs. 3.21 mg/mL for the control Suboxone® tablet. See Tables 6 and 7, pages 24-25 of the instant application.

8. The devices of the claimed invention provide a therapeutic amount of buprenorphine by utilizing less than half of the buprenorphine dose as compared to the Suboxone® tablet (which is currently the standard of care). Not only is less than half the therapeutic drug needed to obtain therapeutic levels, but the patient is no longer exposed to the excess buprenorphine. This is significant because exposure to opioid, such as buprenorphine, in the GI tract is associated with side effects such as constipation. Finally, the claimed devices provide enough buprenorphine for effective pain relief and treatment of opioid dependence, while retaining the abuse-deterrent effect of naloxone, should the devices be used abusively (*e.g.*, dissolution and injection).

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made may be punishable by fine or imprisonment, or both, and that such willful false statements may jeopardize the validity of this Application for Patent or any patent issuing thereon.

Dated: 2/22/13

Signature: _____

Niraj Vasisht, PhD